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Synthesis and Polymerisation of Isotopically Labelled Methacrylate Based Monomers

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Prash Sinnathamby

Ph.D Thesis

Department of Chemistry

University of Durham

2000

19 SEP 2001

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DECLARATION

The work contained in this thesis was carried out in the Department of Chemistry at the University of Durham between October 1996 and September 1999 by the author, unless otherwise indicated. It has not been previously submitted for a degree at this or any other University.

Abstract

This thesis is concerned with the synthesis and polymerisation of isotopically labelled methacrylate based monomers.

Chapter 2 describes the preparation of methyl [2-^{13}C]-and [3-^{13}C]-methacrylate *via* a Wittig-Horner type reaction and a diethyl malonate route respectively. The results of the free radical polymerisation of these monomers are discussed in Chapter 4. The presence of ^{13}C-isotope in the resultant polymer enhanced the low intensity signals from the end groups in the ^{13}C-NMR. However, more importantly, this study allowed us to investigate the presence of head to head links by observing for the first order ^{13}C-^{13}C coupling from the two quaternary carbons in the polymer of methyl [2-^{13}C]-methacrylate. The findings of this study are reported in Chapter 4, Part 1.

Chapter 3 describes the preparation of methyl [α-^{13}C]-(hydroxymethyl)-[3-^{13}C]-acrylate, [$^{13}C_2$]-MHMA and methyl [α-$^{2}H_2$]-(hydroxymethyl)-[3-$^{2}H_2$]-acrylate, [$^{2}H_4$]- MHMA monomers. The copolymeristion with methyl methacrylate and subsequent lactonisation are reported in Chapter 4, Part 2. In the ^{13}C-NMR spectrum of lactonised MMA/[$^{13}C_2$]-MHMA copolymer, the signals from any residual $^{13}CH_2OH$ groups were absent, indicating that lactonisation was complete under the conditions described.

Chapter 5 describes the preparation of fluorinated and non-fluorinated phosphonate based methacrylate monomers to study their potential as ionic materials and extend their application as a fire retarding material. However, attempts to polymerise these monomers by either free radical or anionic methods met with little success. The successful preparation of a polymer from a non-phosphonate based methacrylate monomer indicates that perhaps the phosphonate moiety inhibits the polymerisation by being a radical acceptor.

Acknowledgements

I take this opportunity to express my appreciation and gratitude to my supervisor, Prof. D. O'Hagan, for his help, encouragement and support throughout this research. I wish him a very successful career with his new appointment at the University of St. Andrews.

I would also like thank Dr M. Chisholm, Ineos Acrylics (formally ICI Acrylics) for funding this research in the form of an EPSRC Case Award and Drs A. Slark and P. Eustace for attending the quarterly meetings and contributing to our discussions. I am also indebted to Alan Bunn for carrying out the NMR analysis of my isotopically labelled polymers and more importantly assigning all those peaks. My thanks are also extended to my friends and colleagues at Ineos Acrylics for providing me with a pleasant and enjoyable working environment.

At the University of Durham, I would like to acknowledge the technical support staff who carried out the numerous NMR, GC-MS, Elemental and GPC analysis of my samples. Many thanks are also due to the glass blowers, Gordon, Ray and young Malcolm and to Jim, Joe and Elizabeth in the stores, for their contribution. I would also like to wish my friends in the research group and in the halls of residence success their new careers and thank them for being good friends with me and making my study at Durham very enjoyable.

I am also undoubtedly obliged to Dr C. W. Rabener and Mr P. T. Wombell, Vantico Ltd (formally Ciba Performance Polymers) for giving me leave from work to complete my thesis. Your help is very much appreciated.

Finally, a big thank you to my parents and my sister for being very supportive throughout my studies and for having the faith in me that I would complete my Ph.D. thesis and submit on time.

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Abbreviations

ACP	Acetone cyanohydrin process
Ac	acetyl
AIBN	Azobis(isobutyronitrile)
aq.	Aqueous
n-BuLi	*n*-Butyl lithium
CI	Chemical ionisation
Conc.	Concentrated
d	Doublet
DABCO	Diazobicyclo[2.2.2] octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DMSO	Dimethyl sulphoxide
dq	Doublets of quartet
DHU	Dicyclohexylurea
DMAP	*N,N*-dimethyl aminopyridine
DSC	Differential scanning calorimeter
EA	Ethyl acrylate
EI	Electron impact
EHMA	Ethyl α-(hydroxymethyl)acrylate
EMA	Ethyl methacrylate
equiv.	Equivalent
EPSRC	Engineering and Physical Research Council
GC	Gas chromatography
GPC	Gel permeation chromatography
h	Hour(s)
HCl	Hydrochloric acid
IR	Infra-red
LDA	Lithium di*iso*propylamide
Lit.	Literature

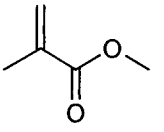
M	Molar concentration (mol.dm-^{3})
m	Multiplet
MHMA	Methyl α-(hydroxymethyl)acrylate
min.	Minute(s)
MMA	Methyl methacrylate
MS	Mass spectroscopy
m/z	Mass/charge ratio
NMR	Nuclear magnetic spectroscopy
N-^{i}PCA	*N-iso*propylcyclohexylamine
p	Pentet
PMMA	Poly(methyl methacrylate)
r.t.	Room temperature
s	Singlet
sat.	Saturated
t	Triplet
Tc	Ceiling temperature
Tg	Glass transition temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
w/w	weight/weight

Chapter 1

Introduction

1.1 Introduction

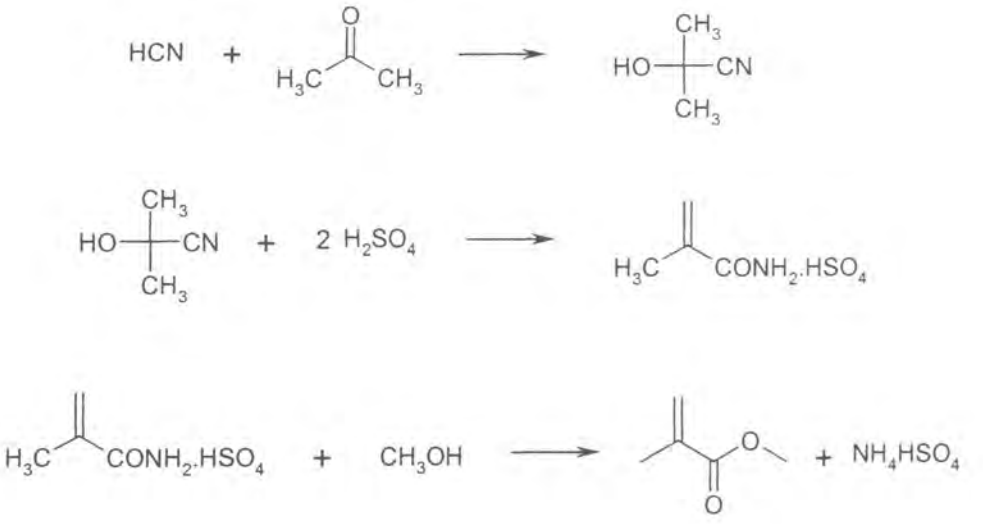
This thesis is concerned with the synthesis and polymerisation of methyl methacrylate (MMA) **1** and related monomers.



1

Interest in acrylates began in 1843 with the first reported preparation of acrylic acid by air oxidation of acrolein (propenal).[1,2] Methacrylic acid was later synthesised in 1865 by the dehydration and hydrolysis of ethyl α-hydroxyisobutyrate.[3] Several years elapsed before methyl and ethyl acrylate were prepared in 1873.[4] However, attempts to polymerise these monomers failed and it was not until 1880 that the preparation of poly(methyl acrylate) was reported by Kahlbaum.[5] In 1901 Rohm was preparing his Ph.D. thesis having studied the remarkable properties of acrylate polymers. His research led the Rohm and Haas Company in Darmstadt, Germany to start producing acrylates in 1927.[6]

Until around the 1930's most of the development focused on acrylate polymers and these polymers were used to laminate safety glass. However, the polymer was considered to be too soft and the search to find a tougher material began. It was found that copolymers of ethyl methacrylate gave the necessary hardness required. This discovery led to the first commercial production of ethyl methacrylate in 1933.[7] During that period, the Rohm and Haas Company polymerised methyl methacrylate (MMA) but were unable to commercialise the product until an economical route to MMA was found. In 1931 the ICI chemist, John Crawford[8,9] discovered the Acetone Cyanohydrin Process (ACP), shown in **Scheme 1**, which emerged as efficient method to prepare MMA.



Scheme 1

The process involves reacting acetone and hydrogen cyanide and feeding the product, acetone cyanohydrin into the reactor where it is treated with excess sulphuric acid, to give methacrylamide sulphate. This intermediate is subsequently reacted with aqueous methanol without isolation in a combined hydrolysis-esterification reaction to give MMA. A schematic representation of the acetone cyanohydrin process is shown in **Figure 1**. Today the acetone cyanohydrin process is still the major method employed to manufacture MMA monomer.

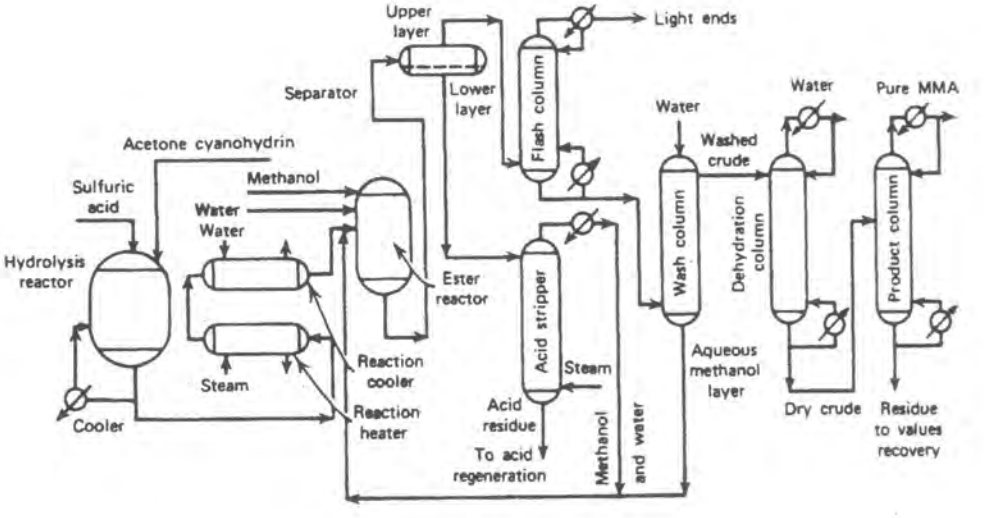
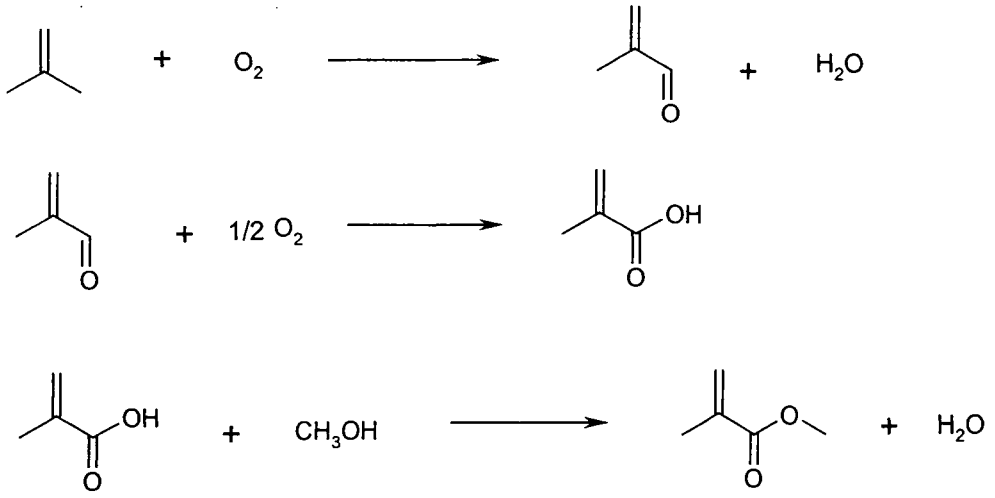


Figure 1 A schematic representation of the Acetone Cyanohydrin Process.[1]

While ICI was developing the new process, the Spitfire fighter plane designers, led by Reginald Mitchell were exploring the possibility of using PMMA for glazing the sliding hoods of their pilots' cockpits. The designers chose PMMA as the polymer had excellent optical and mechanical properties. During World War II, PMMA was exploited as a glazing material and by the end of the war ICI's capacity to produce this material had increased by twenty-fold.

Soon PMMA began to be used in lighting diffusers, car rear lights, signs, beacons and decorative mouldings. Although further applications such as hospital incubators, prismatic lenses and decorative tableware continued to be developed through the 1950's and 1960's, there were limitations to this material. Its applications were somewhat restricted because commercial grade PMMA had a low glass transition temperature (*Tg*~100°C). Much effort was therefore directed at modifying the properties of PMMA with the major challenge being, to obtain a material with a higher *Tg* whilst not compromising the optical clarity of the polymer. During the 1960's and 1970's, the Rohm and Haas Company explored methods to chemically modify PMMA. The company was granted a patent[10] for introducing cyclic imide groups into the PMMA backbone. The resultant polymer was tougher than PMMA and had an enhanced glass transition temperature of about 170 °C due to stiffening of the polymer chain. Other developments included the attempts by Du Pont and Rohm and Haas to generate rubber roughened PMMA with up to 10-fold increase in impact strength.[11]

The Acetone Cyanohydrin Process is still a popular method to manufacture MMA, however, companies such as Nippon Shokubai Kagaku, Mitsubishi Rayon and Asahi Chemical have developed and exploited the C_4 oxidation process[1] shown in **Scheme 2**.



Scheme 2

The method involves a two stage oxidation, starting with isobutylene as the raw material. Oxidation gives isobutenal which is further oxidised to methacrylic acid and converted to the corresponding methyl ester. In 1992 the world-wide production of MMA reached 1.54 million tons. Methyl methacrylate is in economic terms the most important methacrylic acid ester available commercially and its principle producers are Rohm and Haas, and ICI.

Free radical polymerisation is the most commonly employed method in industry for the polymerisation of MMA. Other methods include group transfer polymerisation (GTP)[12], anionic or metal mediated polymerisations. Free radical polymerisation can be carried out under relatively undemanding conditions and is tolerant to small quantities of impurities. The polymerisation can be conducted without removing the stabilisers added to the monomer for storage and in the presence of trace amounts of oxygen or in solvents that have not been rigorously dried. These attributes have therefore made this method of polymerisation the favoured method in industry for preparing high molecular weight polymers.

1.2 Thermodynamics of polymerisation

The thermodynamics of polymerisation can be understood by considering the equation below.

$$\Delta G = \Delta H - T\Delta S \qquad (1)$$

In order for the polymerisation reaction to take place, the free energy change ΔG arising from the process of monomer being converted to polymer must be negative. Polymerisation results in net loss in translational entropy as the monomer becomes covalently bonded to form the polymer chains. The change in entropy, ΔS is therefore negative and is of the magnitude 100 $Jmol^{-1}$. The penalty for polymerisation in terms of change in entropy is large and unfavourable. However, the polymerisation of vinyl monomers such as methyl methacrylate, styrene, vinyl acetate etc. all involve the breaking of weaker π bonds and forming of stronger σ bonds and this is exothermic, overall. The enthalpies of polymerisation ΔH_p are shown in **Table 1** for some vinyl monomers. The ΔH_p values range from -35.2 $kJmol^{-1}$ in the case of α-methylstyrene to -155.5 $kJmol^{-1}$ for tetrafluoroethylene. Under normal polymerisation temperatures, the $T\Delta S$ term is less significant than the ΔH. ΔG is then negative and favours polymerisation. However, there is a temperature at which equilibrium conditions are reached where $\Delta H = T\Delta S$ and any further increase in temperature makes ΔG positive and disfavours polymerisation. There is therefore an equilibrium point when $\Delta H = T\Delta S$ and $\Delta G = 0$.

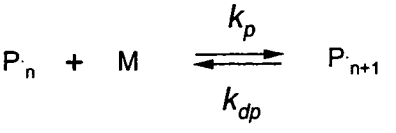
The enthalpy of polymerisation varies according to the monomer. The factors which account for these variations are; the energy difference between monomer and the polymer, substituent interactions and polar or secondary bonding effects. The most significant contribution to ΔH_p arises due to steric factors.

Monomer	$-\Delta H_p^*$ ($kJmol^{-1}$)
Styrene	68.5
α-Methylstyrene	35.2
Isobutene	52.7
Methyl acrylate (MA)	78.2
Methyl methacrylate (MMA)	58.1
Methyl ethacrylate	32
Ethyl methacrylate (EMA)	58.9
Vinyl acetate	89
Vinyl chloride	95
Tetrafluoroethylene	155.5

Table 1 Polymerisation enthalpies for some vinyl monomers.[1]

*Calorimetric

The polymerisation is potentially an entropically favoured reversible process and becomes more likely with increased temperature. The reversible nature of the reaction is illustrated in **Scheme 3**.



Scheme 3

The temperature at which the rate of propagation matches the rate of de-polymerisation is the ceiling temperature, T_C and above this temperature no polymer is formed. At the ceiling temperature the rate of polymerisation is zero and therefore;

$$K = \frac{k_p}{k_{dp}} = \frac{1}{[M_e]} \qquad (2)$$

where M_e is the equilibrium monomer concentration.

The expression for the ceiling temperature can be written as follows,

$$T_c = \frac{\Delta H_p}{\Delta S_p^\circ + R\ln[M_e]} \qquad (3)$$

The ceiling temperature is dependent on the monomer concentration. The ΔH_p and ΔS°_p terms can depend on steric factors. In general α-methyl substitution lowers ΔH_p and this is indeed the case for styrene *vs* α-methylstyrene and MA *vs* MMA *vs* EMA. The lowering of ΔH_p reflects the increased difficulty in forming bonds to tertiary centres. The entropy term is also thought to be an important factor and introducing an α-methyl group usually generates a polymer that is rigid and more ordered from the corresponding vinyl monomer. Therefore, MMA would be expected have a larger ΔS°_p than MA. Some values for ceiling temperatures are reported for certain monomers in the **Table 2**.

Monomer	T_C (K)
MA	354
MMA	493
Styrene	583
α-Methylstyrene	334

Table 2 Ceiling temperatures for some common monomers.

1.3 Molecular weight distribution

Free radical polymerisation involves repeated addition to the monomer and regeneration of active radical centres that are terminated or transferred. The random nature of the growth process produces polymer chains of different lengths and such a distribution in chain length cannot be described by a single molecular weight. Such polymer systems are characterised by molecular weight distributions and the associated averages. Molecular weight distribution data is represented usually on a continuous curve where molecular weight or radius of gyration is plotted on the ordinate and the number or

weight of polymer molecules or the refractive index of their solution on the abscissa. Molecular weight distribution in general is difficult to measure and therefore more than one average is generally reported. The number average molecular weight $\overline{M}_n$ is defined as,

$$\overline{M}_n = \frac{\Sigma N_i M_i}{\Sigma N_i} = \frac{\Sigma W_i}{\Sigma W_i / M_i} \qquad (4)$$

where, N_i is the number of molecules of species i of molecular weight Mi. The number average molecular weight is obtained by a method that counts the number of polymer molecules present in a sample and can be determined by osmotic pressure.

The other commonly used average is the weight average molecular weight $\overline{M}_w$ and is represented by the following equations. It can be measured by light scattering, a method that is sensitive to the weight of the polymer molecules. The weight average corresponds to the mean of the weight distribution and is related to the number data by the following equations.

$$\overline{M}_w = \frac{\Sigma W_i M_i}{\Sigma W_i} = \Sigma w_i M_i \qquad (5)$$

$$\overline{M}_w = \frac{\Sigma N_i M_i^2}{\Sigma N_i M_i} \qquad (6)$$

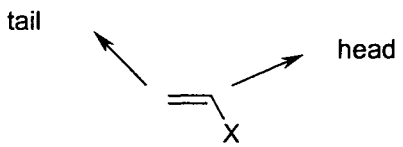
A higher average, the $(z+1)$ average for a polymer can be given by,

$$\overline{M}_{z+1} = \frac{\Sigma N_i M_i^4}{\Sigma N_i M_i^3} \qquad (7)$$

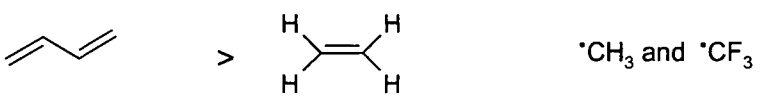
The breadth of the distribution of the chain lengths in a polymer sample is measured by the polydispersity index and at best is only a rough guide to the range of the molecular sizes present. The polydispersity of the sample is given by $\overline{M}_w / \overline{M}_n$.

1.4.1 Radical stabilisation and steric effects

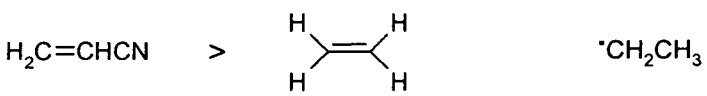
Radical reactions have particular characteristics which account for some of the observations encountered during polymerisation. The site of attack of a radical is determined by the stability of the newly formed radicals, polar factors and steric effects. In the mid 1940's Kharasch *et al*[13] proposed that addition occurs mainly at the least substituted carbon.



Tedder *et al*[14] compared the relative rates and regioselectivity of a number of radicals between ethylene and monosubstituted ethylenes. It was noted that the addition of $^{\cdot}CF_3$ and $^{\cdot}CH_3$ proceeded much faster to butadiene than ethylene and it was rationalised that in butadiene, the π orbital overlap with the half filled atomic orbital of the radical stabilised the radical by resonance.

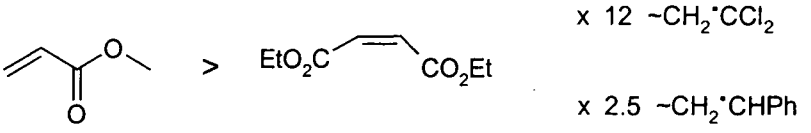


In the case of acrylonitrile the rate of tail addition was again faster than reaction with ethylene.

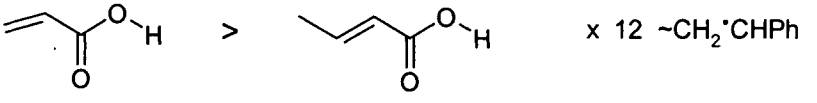


Again resonance stabilisation and polar effects are thought to be the major factors responsible for the enhancement of the rate in acrylonitrile. To date there are only a few exceptions and these include the addition of $^{\cdot}CF_3$ and $^{\cdot}CCl_3$ radicals to CF_2=CHCl. The addition in this case takes place to the CF_2 end because fluorine is smaller than chlorine. Fluorine is only slightly larger than hydrogen and addition is therefore determined on steric grounds. Walling[15] studied the effects of such substituents and one of his

examples included comparing the reactivity of methacrylate and ethyl fumarate. The former is 12 and 2.5 more reactive towards ~CH_2'CCl_2 and ~CH_2'CHPh respectively.



Reactivities also differ greatly when acrylic acid is compared with crotonic acid, the former being 12 times more reactive towards ~CH_2'CHPh. Such reactions greatly favour tail addition on steric grounds.



Vinyl monomers carry steric strain and this is reflected in the values of enthalpy of polymerisation ΔH_p. There is a clear difference between the values of ΔH_p of 1,1 disubstituted and monosubstituted vinyl monomers. The enthalpy of polymerisation for methyl methacrylate is -54.4 kJmol^{-1}, whereas the value for methyl acrylate is -78.2 kJmol^{-1}, a difference of 23.8 kJmol^{-1}. Therefore, the methyl group inhibits polymerisation. In the case of α-methylstyrene, ΔH_p = -35.1 kJmol^{-1} compared with -68.6 kJmol^{-1} for styrene, 33.1 kJmol^{-1} lower. Although these values suggest a small contribution to stabilisation arising from conjugation, it illustrates the steric strain built into the chain as they polymerise.

Regioselectivity is also dependent on the size of the attacking radical. A study by Tedder and Walton[16] reported that there is preferential attack at the least substituted carbon as the size of the radical increases, see **Table 3**.

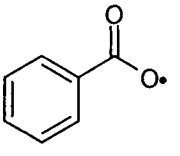
Radical	$_{\alpha}CH_2=_{\beta}CHF$, ratio α:β
$^{\cdot}CF_3$	1:0.1
$^{\cdot}CF_2CF_3$	1:0.06
$^{\cdot}CF_2(CF_3)_2$	1:0.02
$^{\cdot}CF_2(CF_3)_3$	1:0.005

Table 3 Regioselectivity of fluoroalkyl radicals to vinyl fluoride at 164 °C.

1.4.2 Polar contributions

The rate of a free radical reaction is influenced by the polar contribution to the transition state.[17] In the case of 1,1-difluoroethylene, where the C-F bond is highly polarised, the rate of head addition is expected to be enhanced by nucleophilic radicals, whereas tail addition rates are favoured by electrophilic radicals. Tedder and Walton[16] studied the reactivity of tetrafluoroethylene and ethylene with a number of radicals, $^{\cdot}CH_3$, $^{\cdot}CH_2F$, $^{\cdot}CHF_2$ and $^{\cdot}CF_3$. Increase in fluorine substitution progressively made the radical more electrophilic in character. It was observed that the rate of addition of the $^{\cdot}CF_3$ radical to tetrafluoroethylene was slow while the rate was greatly enhanced by the nucleophilic $^{\cdot}CH_3$ radical. The reactivity of polar alkenes towards the ethyl radical has been studied by Bloor *et al.*[18] The rate of addition to the monomer CH_2=CH-R was found to be enhanced by polar substituents in the order R = -CN > Ph ~ CH_2=CH- > $MeCO_2$- > n-C_4H_9O- > alkyl.

The reactivity of MA and MMA towards electrophilic benzoyloxy radicals **2** has been studied by Moad *et al.*[19]



2

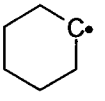
The rate constants for tail (k_T) and head addition (k_H) of the benzoyloxy radical are reported relative to tail addition to MA.

$k_{T(MA)} = 1.0$ $\quad$ $k_{T(MMA)} = 4.5$

$k_{H(MA)} = 0.2$ $\quad$ $k_{H(MMA)} = 0.35$

As can be seen from the rate constants, selectivity and the rate of addition of electrophilic radicals to MMA is enhanced relative to MA. This is due to the electron donating nature and steric influence of the methyl group of MMA

The converse is observed for the same system when addition of nucleophilic cyclohexyl radicals **3** are considered.[20]



3

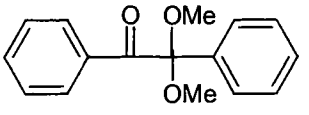
$k_{T(MA)} = 1.0$ $\quad$ $k_{T(MMA)} = 0.71$

$k_{H(MA)} = 0.002$ $\quad$ $k_{H(MMA)} = \leq 0.001$

The electron donating methyl substituent and steric influence retards head addition of nucleophilic radicals when compared with MA The addition of the cyclohexyl radical to the tail end of MMA is retarded by ~30 % due to the methyl substituent.

1.5.1 Initiators

There are a number of common initiators for free radical polymerisation. These comprise the widely used diazo compounds and the peroxides. Others include, photochemical initiators used mainly for curing or crosslinking such as α,α'-dimethoxy-α–phenylacetophenone **4**, more commonly known as benzoin ethers or aryl alkyl ketones and acylphosphine oxides **5**.



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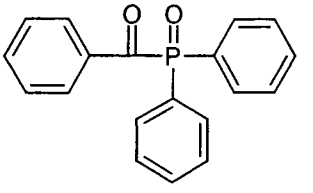

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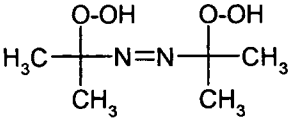
For polymerisations carried out at low temperatures, multifunctional initiators such as α–hydroperoxy diazenes **6** are used. The fragmentation of the initiator generates both alkyl and hydroxy radicals capable of initiating the polymerisation under relatively milder conditions.

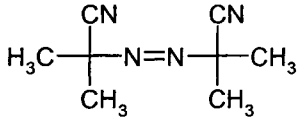


6

There are numerous initiators available for use in free radical polymerisation. During this research azobis(isobutyronitrile) was employed as the initiator in all of the polymerisation reactions and therefore the detailed discussion will be limited to the azo compounds.

1.5.2 Azo initiators

This class of initiators can be subdivided into dialkyldiazenes and dialkyl hyponitrites. The dialkyldiazenes are symmetrically or asymmetrically substituted, with the majority symmetrically substituted. The most widely used is 2,2'-azobis(2-methylpropanenitrile) **7**, more commonly known as azobis(isobutyronitrile) or AIBN. Others include 1,1'-azobis(1-cyclohexanenitrile) **8**, 2,2'-azobis(2-methylbutanenitrile) **9** and 4,4'-azobis(4-cyanovaleric acid) **10**.



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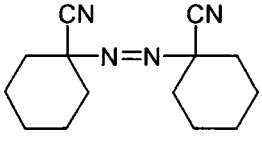

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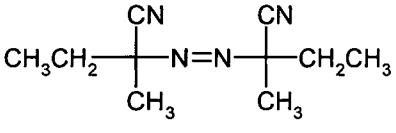

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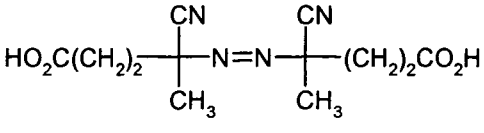

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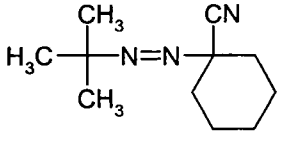
Asymmetric dialkyldiazene, *t*-butylazocyclohexanecarbonitrile **11** is used for its enhanced solubility in organic solvents and *t*-butylazoformamide **12** is used in applications where the initiation temperatures are high.



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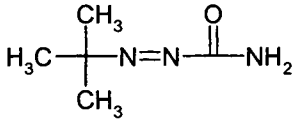
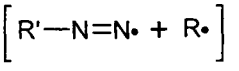


12

Dialkyldiazenes can be induced to undergo either thermal or photochemical decomposition. The kinetics and the mechanism of decomposition of these compounds

has been reviewed by Engel.[21] The decomposition products are two alkyl radicals and liberation of nitrogen (N_2). In some asymmetric dialkyldiazenes it is established that the fragmentation process is not a concerted two-bond cleavage and it is believed to proceed through a diazenyl radical intermediate **13**.[22]



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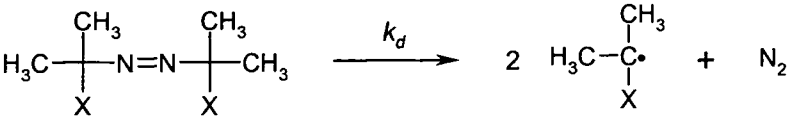
The thermal decomposition rate k_d of dialkyldiazenes **14** is dependent on the α-substituent X[23], see **Scheme 4**.



14

Scheme 4

The rate k_d is reported to increase with groups which are capable of stabilising the alkyl radical and it is therefore expected to be higher with compounds bearing aryl substituents than those with alkyl substituents. This is found to be the case and k_d increases in the following order; CH_3 <-OCH_3 <-SCH_3 <-CO_2R ~ CN <-Ph <-$CH{=}CH_2$. The decomposition rates are also dependent on temperature and have been studied by Bevington and Wahid[24]. For AIBN in toluene values have been obtained at various temperatures and are shown in the **Table 4**. Steric factors[25] and ground state strain[26] are also known to play an important part in the reactivity of these compounds.

Temperature (°C)	10^5 x k_d (s^{-1})
70	4
80	15
90	49
100	160
105	261

Table 4 Rates of decomposition of AIBN at various temperatures.

1.5.3 Cage reactions

The decomposition of the initiator in the case of AIBN and the majority of other initiators produces two radicals capable of propagation, however, these radicals can react together or with any other species present in the medium. Such reactions are dependent on the rate of diffusion of the radicals through the solvent and therefore viscosity of the medium plays an important part in controlling such solvent cage reactions.[27,28] Other factors include the size and reactivity of the radicals. The products of cage reaction can sometimes copolymerise with the monomer as in the case of methacrylonitrile.[29,30] These reactions reduce the initiator efficiency and affect polymer properties. Other concerns include toxicity of e.g. tetramethylsuccinonitrile in materials which may be used in food products.[31]

In certain initiators, and in particular benzoyl peroxides 'cage return' is very pronounced and the radicals formed from the process of decomposition, recombine to form the initiator again. However, this only affects the rate of decomposition and does not impact on the efficiency of the initiator. The decomposition rate for AIBN is influenced by the dielectric constant of the medium and k_d is higher for aromatic over hydrocarbon solvents.[32,33,34] Unlike benzoyl peroxide, the decomposition of AIBN is irreversible and solvent viscosity has no effect on k_d, an observation consistent with the absence of cage return in these systems. These processes become more pronounced during the course of the polymerisation as the viscosity of the medium increases. It has

been reported that in polymerisations carried out to low conversions in a less viscous media that the proportion of radicals capable of propagation is between 50-70 %.[35,36]

1.5.4 Primary radical termination

Radicals formed from the decomposition of the initiator are called primary radicals. These may interact with a growing chain or a second primary radical to undergo primary radical termination. Primary radical termination is relatively insignificant because the radicals react rapidly with the monomer and the steady state concentration of propagating chains is typically $\leq 10^{-7}$M and is even lower for the primary radicals derived from the initiator. Primary radical termination is a significant process during high rates of initiation and in polymerisations where low monomer concentrations are employed. If primary radical termination is significant, the rate of initiation of propagating chains will no longer be proportional to the initiator concentration.

1.5.5 Chain transfer to initiator

Chain transfer to the initiator (C_I) occurs when a propagating radical reacts with the initiator. If as a consequence of this process an initiator molecule is destroyed, the rate of initiation will decrease rapidly. Dibenzoyl peroxides and other peroxide initiators are well known to chain transfer and typically values of 0.012-0.16 for styrene at 60°C have been obtained as chain transfer constants.[37,38] Values for AIBN are usually lower, C_I is 0.02 for the polymerisation of MMA at 60 °C.[39] Transfer to initiator lowers molecular weight and introduces new end groups into the polymer.

1.6.1 Kinetics of free radical polymerisation

Free radical polymerisation reactions involve generating an active centre that is capable of adding to the monomer. The process has three distinct stages; initiation, propagation and termination. This active centre is capable of subsequent additions and continues until termination. A kinetic expression for the rate can be developed for each stage, however, the following assumptions are made in deriving the idealised kinetic expressions;

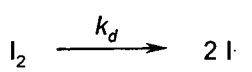
(1) The velocity coefficients are independent of radical size and therefore the rate constant for each propagating step is the same. It follows that transfer coefficients k_{tM} (transfer to monomer), k_{tS} (transfer to solvent) and similarly termination coefficients k_{tc} (termination by combination), k_{td}.(termination by disproportionation) are all independent of the number of monomer units that have added to the initiator.

(2) A steady state is established for all the radical intermediates.

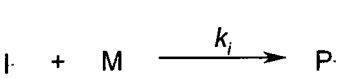
(3) The mean kinetic chain length is large.

1.6.2 Initiation

The initiation takes place in two distinct stages. The decomposition of the initiator to give two radicals,



and then the attack of the radical with the monomer.



A certain proportion of the radicals formed by the decomposition of the initiator are lost through cage reactions, primary radical termination, transfer to initiator and any other side reactions capable of consuming the initiator or the initiator derived radicals. The

number of radicals formed capable of propagation, is proportional to f, the initiator efficiency and can be expressed by the equation below.

$$f = \frac{\text{[rate of initiation of propagating chains]}}{n\ \text{[rate of initiator diappearance]}} \qquad \textbf{(8)}$$

The rate of initiation for thermally initiated polymerisation can be expressed by the equation below. A factor of two is introduced because two radicals, potentially capable of initiation are produced from decomposition of the initiator.

$$R_i = 2k_d f [I_2] = d[P^{\cdot}]/dt \qquad \textbf{(9)}$$

1.6.3 Propagation

Once chain initiation has occurred, iterative addition of the monomer takes place. Growth of the polymer chain occurs exclusively by head to tail addition and can continue to build a polymer comprising of 10^2 to 10^6 monomer units.

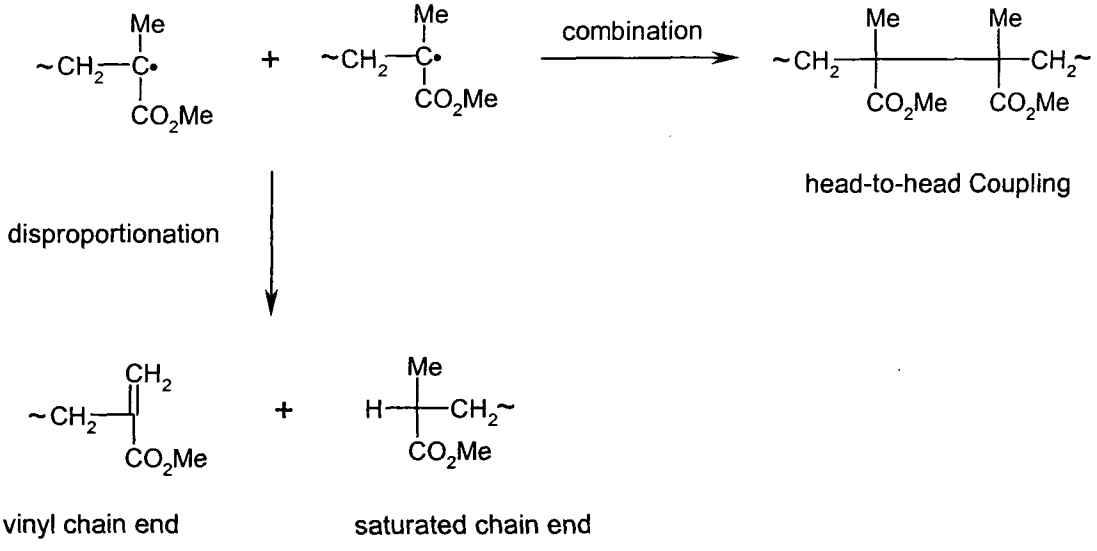
On the assumption that the monomer is primarily consumed in the propagating steps and that the kinetic chain is large, an expression for the rate of propagation can be written as follows;

$$R_p = k_p[P^{\cdot}][M] \qquad \textbf{(10)}$$

The lifetime of the propagating radical, $P^{\cdot}$, is short and its concentration is low at any particular time. In writing an expression for propagation it is assumed that the rate of the bimolecular reaction for each step is the same and that it is independent of the chain length. For chains longer than twenty monomer units this is found to the case,[40,41] however, there is good experimental evidence to indicate that k_p for the early steps is greater and progressively slows to a plateau at about twenty.[42,43,44]

1.6.4 Termination

Termination of propagating chains may occur by either combination or disproportionation as illustrated in **Scheme 5**.



Scheme 5

Termination by combination of two radicals introduces a head-to-head linkage into the polymer and the rate of formation of the 'dead' polymer is given by $1/2k_t[P^{\cdot}]^2$. This is discussed in greater detail in chapters 2 and 3. Disproportionation involves a propagating chain abstracting a hydrogen radical from another growing chain to give a 'dead' polymer and an unsaturated chain. The terminal methylene group formed is potentially reactive and capable of re-initiation. Disproportionation is the predominant method of termination during the polymerisation of MMA and principally involves the abstraction of the hydrogen from the methyl group over the methylene group.[45] The rate of the disproportionation reaction is given by $k_t[P^{\cdot}]^2$.

In homogeneous polymerisations, the lifetime of a growing radical is shorter than the period over which the rate of propagation is measured. During this period there is no appreciable change in concentration of the initiator and rate of initiation remains relatively unaffected. Therefore, during this period little monomer consumption takes place and any contraction in volume accompanying polymerisation is too small to affect

concentrations. A steady state is established very early in the polymerisation and the rate of initiation and termination become equal and remains so. The overall kinetic expression for the rate of termination is given by;

$$R_t = 2k_t [P^{\cdot}]^2 \qquad (11)$$

1.6.5 Kinetic chain length and degree of polymerisation

The mean kinetic chain length ν is defined as the mean number of monomer molecules that have polymerised as a consequence of a single act of initiation and an expression of the following form can be written.

$$\nu = R_p/R_i = R_p/R_t = k^2_p [M]^2/2k_t R_p \qquad (12)$$

The kinetic chain length is given by the ratio of the polymerisation rate to the initiation rate or to the termination rate as both initiation and termination rates are equal. The kinetic chain length is inversely proportional to the rate of polymerisation. An increase in temperature, increases the rate of polymerisation and consequently decreases the kinetic chain length. It follows that the kinetic chain length is inversely proportional to the radical concentration and therefore the chain length is short for polymerisations initiated with high levels of initiator and vice-versa.

The number average degree of polymerisation $\overline{X_n}$ is the average number of monomer units in a polymer chain and is related to the kinetic chain length. The degree of polymerisation depends on the mode of termination and if the propagating radicals terminate by coupling then the polymer chain is composed of two kinetic chain lengths and can be written as follows.

$$\overline{X_n} = 2\nu \qquad (13)$$

If however the chains terminate by disproportionation the number average degree of polymerisation is equal to the kinetic chain length and is given by,

$$\overline{X_n} = \nu \qquad (14)$$

The number average molecular weight of a polymer can be written as follows,

$$\overline{M_n} = M_o \overline{X_n} \qquad (15)$$

where M_o is the molecular weight of the polymer.

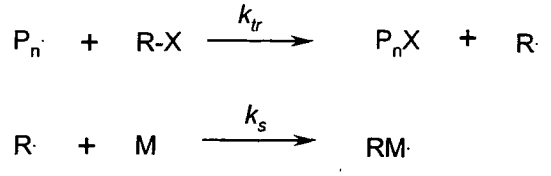
1.7 Bulk polymerisation

Polymerisation carried out in the absence of solvent allows for the formation of high molecular weight polymers in a relatively short time period. Due to the absence of solvent the rate of polymerisation is generally higher in bulk polymerisation and there is a rapid increase in rate towards the end of the reaction. This *auto-acceleration* results in increased viscosity and the phenomenon is termed the *Trommsdorff-Norrish* or *gel effect*. Under these conditions the steady state kinetics approximation cannot be applied.

As the viscosity increases, the steps involved in the polymerisation reaction become diffusion controlled and dependent on the activation energies for that step. The termination step has the lowest activation energy compared with the propagation step and therefore becomes diffusion controlled at low viscosities. Therefore, there is a reduction in the rate of termination and an increase in the number of propagating radicals. As the polymerisation reaction is exothermic, the release of heat increases the rate of initiator decomposition and therefore increases the rate of polymerisation.

1.8.1 Chain transfer

In 1937, Flory reported the principles of chain transfer reactions in radical polymerisation.[46] Chain transfer involves a propagating chain P_n· reacting with a transfer agent R-X where X may be a halogen atom or any other group. The process involves the transfer of the group X to the propagating chain and then generation of a new radical R·. The radical R· formed re-initiates polymerisation by reacting with monomer M. **Scheme 6** illustrates the transfer process, where k_{tr}= transfer constant for the first step and k_S = re-initiation constant.



Scheme 6

If chain transfer proceeds as depicted above, the mean degree of polymerisation decreases and the kinetic chain length increases, assuming that R-X is not a terminated polymer. Unless there is a reduction in the reactivities at the radical sites, the overall rate of polymerisation will remain relatively unaffected in this conventional transfer process.

If the reactivity of radical R· with monomer M is less than that of the propagating radical P_n·, the concentration of R· will increase as will termination. Depletion of [R·] decreases the rate of polymerisation with a consequent decrease in the kinetic chain length. Reactions of this type are called degradative chain transfer reactions. For example in methyl acrylate and vinyl acetate where the rate constant for re-initiation is less than the rate constant for polymerisation ($k_S<k_p$), retardation is more likely than in styrene and methyl methacrylate, which have lower k_p values.

The chain transfer agent may be a substance that is added to the system or a species present within the system. A transfer agent may be added to a particular polymer system to control molecular weight, the rate of polymerisation and also to create new

end groups. In the absence of any added chain transfer agents, chain transfer may take place with the monomer, solvent, polymer or the initiator.

The influence on the number average degree of polymerisation $\overline{X_n}$ can be estimated by the Mayo equation below,

$$\frac{1}{\overline{X_n}} = \frac{1}{\overline{X_{no}}} + C_S\frac{[S]}{[M]} \qquad (16)$$

where, $\overline{X_{no}}$ is the number average degree of polymerisation formed in the absence of chain transfer agent and C_S is the transfer constant for a particular solvent.[47] This simplified equation assumes that solvent transfer predominates, however, under normal polymerisation conditions, transfer to monomer, polymer, and initiator may take place depending on the nature of the system. Taking this into account, the Mayo equation can be re-written as follows, where C_M, C_I, C_P are transfer constants to monomer, initiator and polymer respectively.

$$\frac{1}{\overline{X_n}} = \frac{2k_t[P.]}{k_p[M]} + C_M + C_I\frac{[I]}{[M]} + C_P\frac{[P]}{[M]} + C_S\frac{[S]}{[M]} \qquad (17)$$

1.8.2 Transfer to monomer

The chain transfer constants to certain monomers C_M are shown in **Table 5**. In general they are lower than other chain transfer constants and do not play a significant role in limiting the molecular weight of the polymer. Chain transfer to monomer involves abstraction of a hydrogen radical by breaking strong C-H bonds, giving rise to relatively small values of C_M.

Monomer	Temperature (°C)	$C_M \times 10^4$
MA[48]	60	0.4
MMA[49]	60	0.1
Styrene[50]	60	0.6
Acrylonitrile[51]	60	0.3
Vinyl acetate[52]	60	1.8
Allyl acetate[53]	80	1600

Table 5 Chain transfer constants to some common monomers.

Notably, however, allyl acetate is particularly susceptible to this type of radical transfer during polymerisation. The homolytic abstraction of the allylic hydrogen is activated by the presence of the double bond and the adjacent ester group. These groups stabilise the radical formed suppressing re-initiation and retarding polymerisation. MMA, however, does not undergo degradative chain transfer and this may be due to its higher reactivity allowing efficient re-initiation. In vinyl acetate the homolytic abstraction of hydrogen generates a radical capable of re-initiation and propagation.

1.8.3 Transfer to solvent

The chain transfer constants for some solvents are reported in the **Table 6** for polymerisation of MMA at 60 °C[54] In general aliphatic hydrocarbons and benzene are not susceptible to these types of reactions as the energy of C-H bond breaking is too high. Halocarbons, however, are known to readily undergo chain transfer due to homolysis of the C-X bonds, whereas toluene has a modest chain transfer constant, due to the stability of the benzyl radical.

Solvent	$C_S \times 10^4$
Benzene	0.04
Toluene	0.20
Acetone	0.20
Ethyl acetate	0.15
Carbontetrabromide	2700
Heptane	1.8 (50 °C)

Table 6 Values of chain transfer constants of solvents for the polymerisation of MMA at 60 °C

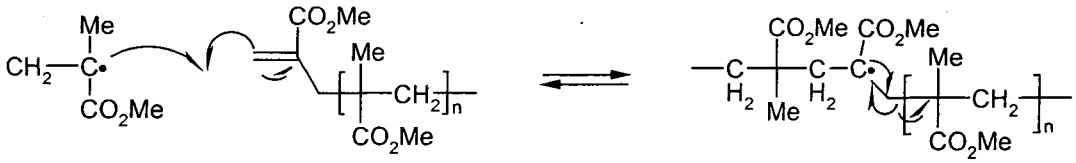
1.8.4 Chain transfer to polymer

Chain transfer to polymer is a significant process at higher conversions and may introduce branches into the polymer chain. Intramolecular reactions or backbiting leads to short branches whereas intermolecular reactions can result in longer branches. Values for C_P are difficult to obtain but they vary with the molecular weight of the polymer. This may account for the wide range of values for C_P reported in the **Table 7**.

Monomer	Temperature (°C)	$C_P \times 10^4$
MMA	60	0.1-360
Styrene	60	1.9-15.8

Table 7 Values of chain transfer for MMA and styrene polymers.

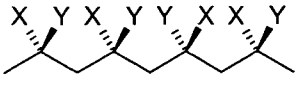
The polymerisation of MMA, generates unsaturated chain ends through disproportionation reactions and it has been reported that oligomeric chains may act as a chain transfer agent to the monomer.[55] These species have also been suggested to act as retarders or inhibitors of radical polymerisation,[56] as shown in **Scheme 7**.



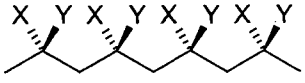
Scheme 7

1.9.1 Polymer stereochemistry

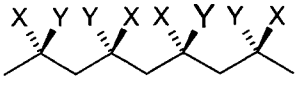
During the polymerisation of disubstituted vinyl monomers, as in MMA, there are two possible stereoregular placements for the monomer during addition to the propagating chain. The stereoregularity of the polymer is therefore determined by the way the monomer orients on addition relative to the propagating chain. In radical polymerisation there is little control over monomer orientation and addition takes place at random, giving an irregular sequence of monomer units within the polymer chain. Such a polymer is termed *atactic*. Atactic polymers in general lack crystallinity and are substantially amorphous.



atactic



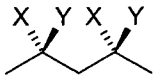
isotactic



syndiotactic

Polymerisation where the monomer orientation is controlled, allow the preparation of more stereoregular polymers. For example by employing Ziegler-Natta catalysts or ionic methods, stereoregular polymers can be prepared. *Isotactic* polymers have the relative configuration of the backbone substituents on the same (*syn*) side and *syndiotactic* polymers have the relative configuration alternating opposite (*anti)* sides. Isotactic polymers are usually crystalline and tend to form helices whereas syndiotactic polymers are generally semi-crystalline and organise themselves as glide planes.

The smallest structural unit in a polymer chain that contains stereochemical information is a dyad. In *meso* (*m*) dyads the two disubstituted carbon centres have the same relative configuration whereas in *racemic* (*r*) dyads they have opposite relative configurations. An atactic dyad is assigned the stereochemical configuration *mr* where as isotactic and syndiotactic dyads are represented as *mm* and *rr* respectively.



meso (m)

racemic (r)

The glass transition temperature (T_g) is influenced by the stereoregularity of the polymer. At this temperature the glasslike and brittle polymer becomes rubbery and soft. The temperature at which this transition takes place is called T_g and it normally takes place over a range of several degrees. The transition is a reversible process and is a function of molecular motion of the polymer chain. Polymers with flexible chains have a low T_g and in polyisoprene for example this value is 200K whereas in atactic PMMA, the energy needed to overcome all the rotational energy barriers in the chain is greater and therefore the polymer has a higher T_g of 378 K. Isotactic PMMA has a T_g of 316K whereas the syndiotactic form is much higher and is 433K.[1]

1.10.1 Copolymerisation

The copolymerisation process involves the reaction of two or more suitable monomers to form a polymer. The copolymer can have modified properties than the parent homopolymers. There are definitions for copolymer structures which depend on monomer reactivity and other factors that are discussed later. The main types of copolymer are;

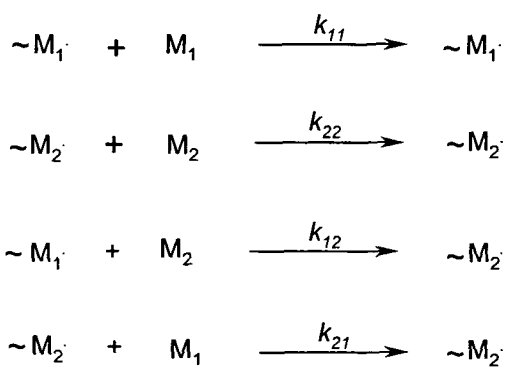
Statistical copolymers: The monomers add to the growing chain in a purely statistical fashion and there is no preference over a particular monomer. The distribution of the monomer units along a polymer chain is therefore random.

Alternating copolymers: The monomer units in the polymer chains are distributed in an alternating fashion ~ABABAB~.

Block copolymers: Each monomer unit is present in blocks along the polymer chain ~AAAABBBAAA~. Controlled polymerisation techniques also allow the preparation of block copolymers with specific tacticities along the polymer chain.

Graft copolymers: Such copolymers are also called branched or comb polymers. Thus, poly(MMA-*graft*-S) indicates that the backbone of the polymer chain is MMA whereas the branch is composed of styrene monomer units.

To successfully synthesise a copolymer, a clear understanding of the factors that control the polymerisation is required. The copolymerisation process can be described by a kinetic scheme involving four principal propagating steps in which the rate constants k_{11} and k_{22} represent self-propagating reactions and k_{12} and k_{21} are the rate constant for cross-propagation reactions as shown in **Scheme 8**.



Scheme 8

The derivation of the Mayo-Lewis equation that describes the copolymerisation process involves making some approximations. They are,

(1) The copolymer composition is determined by the relative rates of each of the four steps above.

(2) The influence of the initiation and termination steps on the rate of monomer consumption is ignored by assuming that the chains are long and the reactivity of the radicals is independent of chain length and is only dependent on the nature of the terminal unit. The rate of consumption of M_1 from the feed is given by,

$$-\frac{d[M_1]}{dt} = k_{11}[M_1][M_1^{\cdot}] + k_{21}[M_1][M_2^{\cdot}] \qquad \textbf{(18)}$$

and similarly, the disappearance of M_2 is described as,

$$-\frac{d[M_2]}{dt} = k_{22}[M_2][M_2^{\cdot}] + k_{12}[M_2][M_1^{\cdot}] \qquad \textbf{(19)}$$

(3) The concentration of the two propagating radicals $M_1^{\cdot}$ and $M_2^{\cdot}$ achieve a steady state conditions such that,

$$k_{12}[M_1^{\cdot}][M_2] = k_{21}[M_2^{\cdot}][M_1] \qquad \textbf{(20)}$$

dividing equations **18** and **19** gives the Mayo-Lewis equation,

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1]}{[M_2]}\left[\frac{r_1[M_1]+[M_2]}{r_2[M_2]+[M_1]}\right] \qquad \textbf{(21)}$$

the quantities r_1 and r_2 are reactivity ratios and are defined as,

$$r_1 = \frac{k_{11}}{k_{12}} \text{ and } r_2 = \frac{k_{22}}{k_{21}} \qquad \textbf{(22)}$$

(4) In deriving such an equation, solvent effects, such as monomer-solvent interactions are ignored.

Copolymer sequence and distribution can be predicted from reactivity ratios of the two monomers. The values of reactivity ratios for comonomers are obtained by analysing the composition of the copolymer formed at low conversions at various $\frac{[M_1]}{[M_2]}$ ratios. If monomer M_1 is more reactive than monomer M_2 then M_1 will form a greater component of the resultant copolymer. The feed mixture will then become depleted in monomer M_1 and composition drift occurs as the reaction progresses.

One of the methods used in predicting reactivity ratios of comonomers involves using the Fineman-Ross equation **23**.[57] F_1 and F_2 are defined as the mole fraction of monomers M_1 and M_2 added to the propagating chain at a given time whereas f_1 and f_2 are the mole fractions in the feed mixture. An equation of the following form as proposed by Finemann and Ross can be written.

$$F_1 = \frac{(r_1 f_1^2 + f_1 f_2)}{(r_1 f_1^2 + 2 f_1 f_2 + r_2 f_2^2)} \qquad \textbf{(23)}$$

If the following parameters are defined as,

$$F = \frac{F_1}{F_2} \text{ and } f = \frac{f_1}{f_2} \qquad \textbf{(24)}$$

then the Finemann and Ross equation can be re-written in a linear form (y = mx + c) as follows,

$$\frac{f(1-F)}{F} = r_2 - \left(\frac{f^2}{F}\right) r_1 \qquad \textbf{(25)}$$

plotting $\frac{f(1-F)}{F}$ *vs.* $\left(\frac{f^2}{F}\right)$ should result in a linear relationship where r_1 is the gradient and r_2 is the intercept.

1.10.2 Reactivity ratios and copolymer composition

The reactivity ratio gives a guide to the copolymer composition. The reactivity ratios for MMA, styrene, ethyl α-(hydroxymethyl)acrylate (EHMA) and methyl α-(hyrdroxymethyl)acrylate (MHMA) are listed in the **Table 8**.

M_1	r_1	M_2	r_2	reference
MMA	0.22-0.64	Styrene	0.28-0.62	58
MMA	1.264	EHMA	1.285	59
Styrene	0.330	MHMA	0.326	60

Table 8 Reactivity ratios for some selected monomers.

In cases where $r_1 \approx r_2 \approx 1$, the monomers show equal reactivity towards the growing polymer chain and there is no preference for a particular monomer. The product is a random copolymer and the relative rates of monomer consumption are determined by the relative monomer concentrations in the feed mixture. In such cases $k_{11} \approx k_{12}$ and $k_{22} \approx k_{21}$, and the Mayo-Lewis equation **21** simplifies to,

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1]}{[M_2]} \qquad \textbf{(26)}$$

Figure 2 shows the variation of F_1 *vs.* f_1 for copolymerisation of monomers with different reactivity ratios. Under the above conditions the copolymer and monomer feed compositions become identical, $F_1 = f_1$ irrespective of the starting f_1 and such a system would be represented by curve I.

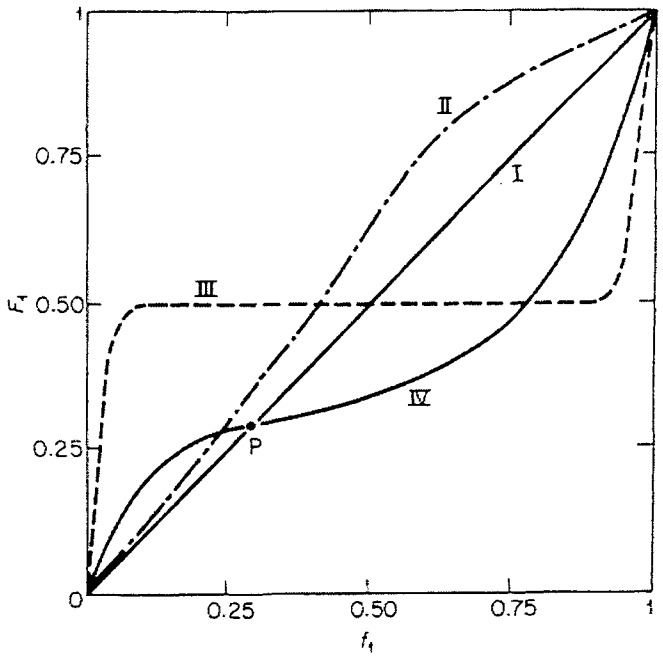


Figure 2 The variation of F_1 *vs.* f_1 for copolymerisation of monomers with different reactivity ratios.

For copolymerisation systems where $r_1 \approx r_2 \approx 0$, the propagating chain expresses a strong preference for cross propagation, $k_{11} \approx k_{22} \approx 0$. The copolymer will then have an alternating distribution of each monomer unit along the developing polymer chain represented by **Figure 2**, curve III. The composition of the copolymer now will be 1:1 regardless of the composition of the monomer feed and the Mayo-Lewis equation **21** can then be rewritten for such a condition as,

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1][M_2]}{[M_2][M_1]} = 1 \qquad (27)$$

Table 8 shows that the for styrene/MHMA copolymer system, $r_1 = 0.33$ and $r_2 = 0.326$. It was reported[60] that for such a system a random copolymer is obtained with a strong tendency towards alternation.

In the majority of copolymerisations, the growing radical shows a clear preference for a particular monomer in the system. This situation arises when $r_1 > 1$ and $r_2 < 1$; $k_{11} > k_{12}$

and $k_{21} > k_{22}$. Under such conditions, the polymer formed will clearly be enriched with monomer, M_1. However in polymer systems where $r_1 r_2 = 1$, both the active centres show the same preference for addition of one of the monomers. This behaviour is called ideal copolymerisation where $\frac{k_{11}}{k_{12}} = \frac{k_{21}}{k_{22}}$ and would be represented by curve I in **Figure 2**. In this case, the Mayo-Lewis equation simplifies to,

$$\frac{d[M_1]}{d[M_2]} = r_1 \frac{[M_1]}{[M_2]} \qquad \textbf{(28)}$$

In an another situation $r_1 < 1$ and $r_2 < 1$; $k_{12} > k_{11}$ and $k_{21} > k_{22}$. Under these conditions the propagating radicals prefer cross-propagation over self-propagation and there is a tendency for alternation as both r_1 and r_2 approaches zero and would be represented by curve IV. The curve passes through P, the point at which $F_1 = f_1$ and represents the azeotropic copolymer composition. A copolymer of constant composition is obtained without the concern of any composition drift.

In cases where $r_1 > 1$ and $r_2 > 1$, there is tendency towards block formation. For the MMA/EHMA copolymer system, reactivity ratios of $r_{MMA} = 1.264$ and $r_{EHMA} = 1.284$ is shown in **Table 8**. These values were estimated by Fernández-Monreal *et al*[59] in tetrahydrofuran solvent using the methods established by Tidwell and Mortimer[61] and indicate that the polymer chains may contain short blocks. The reactivity ratios reported may of course have a solvent dependency as highlighted by Sani *et al.*[62,63] and Johnston *et al.*[64] Harwood recently reported that the values for reactivity ratios in general vary due to the different partition coefficient of monomers in solution.[65] Therefore these values may only be valid for copolymerisations carried out in THF.

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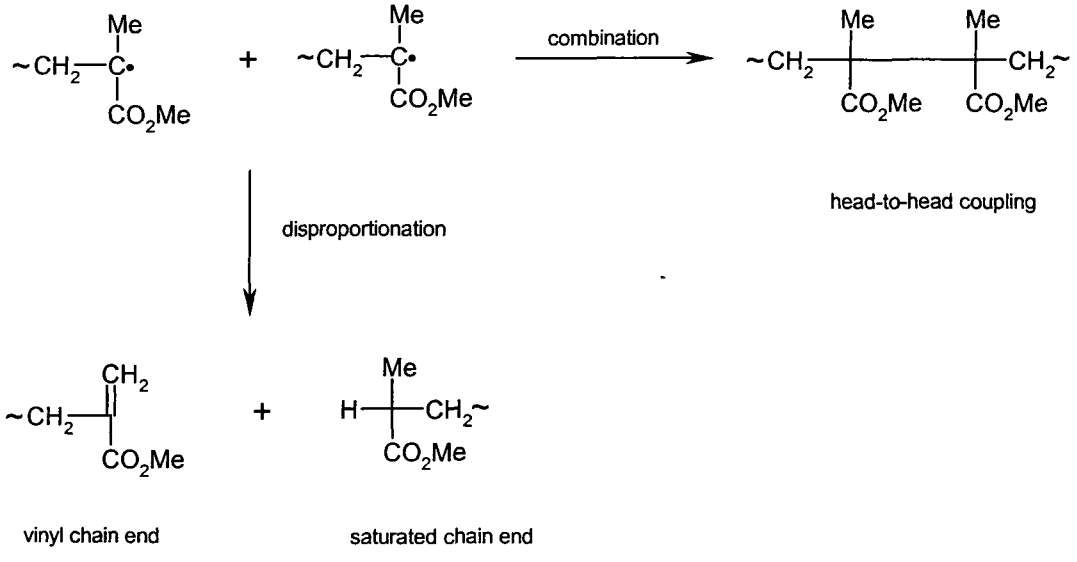
Chapter 2

Synthesis of methyl [2-^{13}C]-and [3-^{13}C]-methacrylate

2.1 Introduction

In free radical polymerisation, the termination of propagating radicals mainly takes place through combination and disproportionation reactions. A combination reaction between two radicals leads to the formation of head-to-head linkages with two quaternary centres vicinal to each other. On the other hand, termination by disproportionation gives rise to an unsaturated vinyl chain end and a saturated chain end as shown in **Scheme 9**.



Scheme 9

Such reactions introduce weak links into the polymer chain and the head-to-head linkages and the vinyl unsaturated chain ends constitute weak links in PMMA. These weak links are responsible for the initial degradation of PMMA. Thermal degradation studies of PMMA oligomers containing head to head links have indicated that these are less stable than the vinyl chain ends.[1] However this is not universally accepted and it has been suggested that the head to head links may be more stable than vinyl chain ends.[2]

In 1986 a study was carried out to investigate structural defects in PMMA. A number of samples were prepared by different polymerisation methods and subjected to thermogravimetric analysis under nitrogen.[3] Until then, there were no previously reported studies describing the effects of head-to-head links on the thermal stability of

PMMA other than the MMA oligomer study described above. Initial experiments compared the thermal behaviour of PMMA generated by radical polymerisation with that of an anionically prepared sample as illustrated in the **Figure 3**. The derivative thermogravimetry results were obtained by taking the time derivative, $d(W/Wo)/dt$ of the ratio of the sample weight, W, to the initial sample weight, Wo.

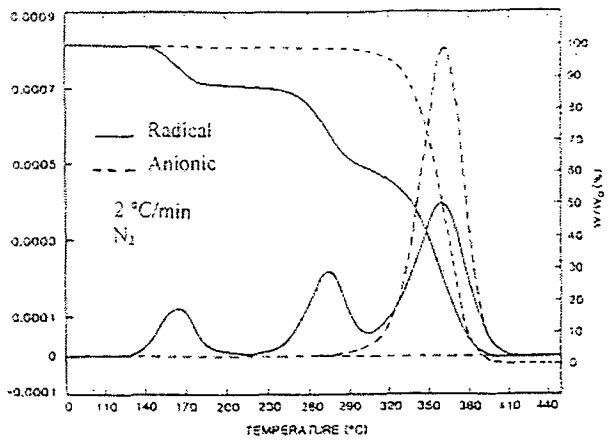


Figure 3 TGA of PMMA prepared by free radical and anionic methods.

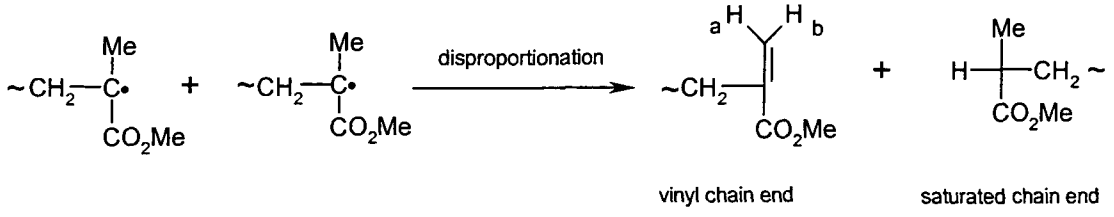
It was observed that in the PMMA sample prepared by an anionic method there was only a single transition corresponding to weight loss initiated at 360°C due to random chain scission which accounts for the rapid weight loss of the polymer. However, in the polymer prepared by radical polymerisation, there were two additional peaks in the TGA trace over which the polymer lost weight. Using various oligomers as models[1], the first transition at 165 °C was attributed to the depolymerisation initiated from the head-to -head links, whereas the transition at 270 °C was assigned to depolymerisation as a result of vinyl chain end initiation. Finally, the transition at 360 °C corresponding to that present in the anionically prepared sample was associated with random chain scission. Clearly therefore, PMMA prepared by radical polymerisation has structural defects not found in anionically prepared material.

In an another study, three PMMA samples A, B and C were prepared by radical polymerisation and the level of unsaturation was estimated from ^{1}H-NMR analysis, see **Table 9**.[3]

Sample	Vinyl chain	Head to Head links
A	~0	-
B	0.034	-
C	0.36	0.28

Table 9 Estimation of vinyl chain ends and head-to-head linkages in free radically prepared PMMA.

^{1}H-NMR analysis of sample C showed that there was no trace of monomer. However, magnification of the spectrum revealed that in the region between 5-7 δ there were two peaks. Both the signals were associated with the methylene protons of the terminal vinyl group, the peak at 5.40 δ being attributed to H_a and the peak at 6.14 δ to H_b. Measuring the intensity of the peaks showed that 36 % of the polymer chains contained the vinyl group at the polymer chain ends. It follows that 72 % of the molecules underwent the disproportionation reaction, as shown in **Scheme 10** and that the remaining 28 % of the molecules would have terminated by a combination reaction resulting in head to head links and saturated chain chain ends.



Scheme 10

The values for A and B were similarly calculated. Samples A and B were prepared using *t*-butyl mercaptan as the chain transfer agent and therefore the main termination mechanism is expected to be a transfer reaction involving the abstraction of a hydrogen to give saturated chain ends. These samples will therefore be expected to have no head-to-head linkages or vinyl chain ends and if present as in sample B would be in small proportions.

All three samples were then analysed by TGA to study the weight loss characteristics. It was reported that both sample A and B did not show any weight loss at ~165 °C, the temperature region attributed to depolymerisation initiated from head to head links, see **Figure 4**.

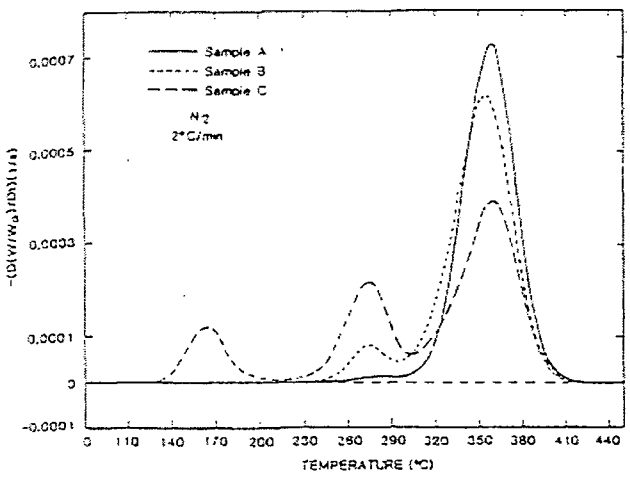


Figure 4 TGA of samples A, B and C containing varying proportions of head-to-head linkages, vinyl chain ends and saturated chain ends.

However, weight loss occurred for both the samples at ~265 °C due to depolymerisation initiated from the vinyl chain end. A weight loss of 2 % occurred for sample A, that had no detectable vinyl chain ends by ^{1}H-NMR analysis and a significantly higher weight loss of 7 % was observed for sample B. For sample C, the peak at 165 °C corresponded to a weight loss of 13 % as a result of the weak head-to head links. The peak at 265 °C was due to the vinyl chain ends and accounted for 25 % of the weight loss. All of the samples underwent random chain scission at ~360 °C. The estimated normalised weight loss for sample C due to head-to-head linkages should be 44 %, however the observed value was only 13 %. It was proposed that radicals created as a result of chain scission at the head-to-head linkages could undergo complete unzipping, terminate, disproportionate or initiate polymerisation of monomers.

Further evidence to support that the least stable structure is the head-to-head link comes from bond dissociation energies. The bond dissociation energy of the head-to-head link is estimated to be 84 kJmol^{-1} lower than that of the C-C bonds of the backbone of the

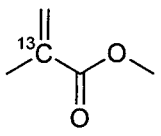
polymer. This arises as a result of steric interactions between the two quaternary centres and the inductive influence of the ester groups. The authors therefore argued that weight loss initiated by chain scissions at head-to-head linkages should occur at a lower temperature than vinyl end initiation.

The most recent investigation of the microstructure of free radically prepared PMMA involved analysis by 750 MHz high resolution ^{1}H-NMR[4]. The PMMA sample was analysed before and after heating to 200 °C under vacuum for 20 minutes. It was anticipated that at 200 °C any head-head links present would have undergone cleavage resulting in the formation of new end groups. However, there were no appreciable changes in the spectra due to the loss of the head-to-head linkages in the polymer sample. A ^{13}C-NMR analysis of such systems has never been reported.

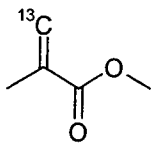
Efforts to study and gain a detailed insight into the microstructure of PMMA have only been successful to a limited extent. The studies have claimed that weak links such as head-to-head linkages and vinyl chain ends are the cause for the early degradation of PMMA. Although such weak links are absent in PMMA prepared by anionic methods these, however, exist in the free radically prepared polymer. Attempts to study PMMA samples using ^{1}H-NMR methods have been unsuccessful in providing any spectroscopic evidence for the presence of head-to-head linkages.

2.2 Aims and objectives

In an effort to explore this fully, the preparation of MMA carrying ^{13}C-labels (99 atom %) became a key objective of this program to investigate the microstructure of PMMA. Routes towards the preparation of methyl [2-^{13}C]-and [3-^{13}C]-methacrylates were investigated.

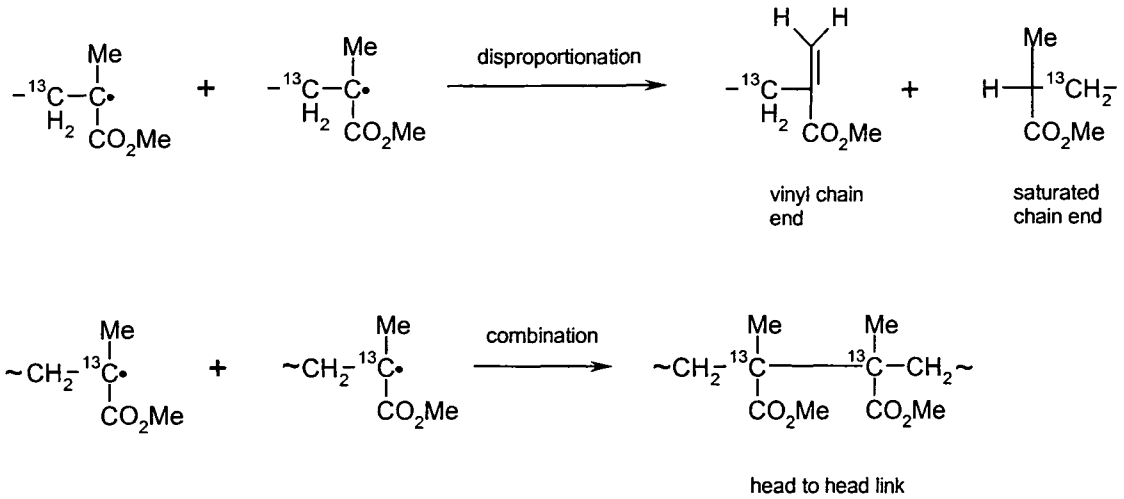


1a



1b

The element carbon consists of stable isotopes ^{12}C and ^{13}C at a 98.9 % and 1.1 % natural abundance respectively. However, the ^{12}C nucleus does not possess a magnetic moment and nuclear magnetic resonance spectroscopy of carbon compounds is restricted to the magnetic ^{13}C nucleus which has a spin I=1/2. The low natural abundance of the ^{13}C nucleus makes ^{13}C-NMR spectroscopy less sensitive and detection more difficult. In general, low intensity signals from end groups and ^{13}C-^{13}C coupling from the head to head links are difficult to detect without ^{13}C enrichment as their statistical frequency is low. Introduction of ^{13}C isotope into PMMA, would enhance these low intensity signals and therefore make detection easier, see **Scheme 11**.



Scheme 11

In designing a synthetic route to a particular isotopically labelled compound the main limiting factor is the availability of a suitable isotopically labelled starting material and the high costs that are associated with these materials. It is therefore desirable to have high yielding steps in the synthetic route to a particular target and it is normal practice to explore the different routes that are available to that compound with unlabelled materials. Purification of the product often results in loss of material and the methods used depend on the quantity of material synthesised. Chromatographic techniques are usually adequate when small amounts of material are prepared, whereas careful distillation is preferred for the purification of larger quantities of labelled products.

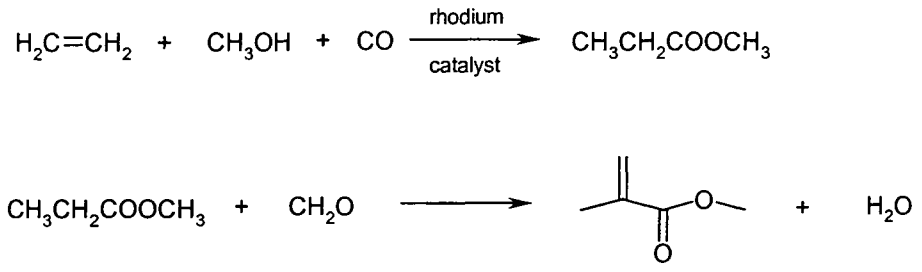
2.3 Review of industrial routes to methyl methacrylate

Much of the synthetic methodology developed for the preparation of MMA took place between 1930's and 1960's. The most common method used to prepare MMA is presently through the ACP developed by ICI during the 1930's, however, hydrogen cyanide used in the manufacture of the monomer by this route is becoming somewhat limited. Hydrogen cyanide is a by-product produced during the manufacture of acrylonitrile. In recent years, acrylonitrile has suffered slower market growth than MMA, therefore supplies of hydrogen cyanide have decreased with a proportional increase in costs. The acetone cyanohydrin route also produces large quantities of waste acid and with increasing concerns regarding environmental pollution there is a need for an alternative method to manufacture MMA. Various efficient, cheaper routes to MMA have been developed which produce less waste material and are more environmentally friendly. The C_4 oxidation process (discussed in chapter 1) is already in use with companies such as Nippon Shokubai Kagaku, Mitsubishi Rayon and Ashai Chemical. The other routes that are available for the manufacture of MMA are discussed below.

2.3.1 Propionate-formaldehyde route

Ethylene has been reported to react with carbon monoxide and methanol to produce methyl propionate in the presence of a rhodium catalyst as shown in **Scheme 12**.[5] The methyl propionate formed is then treated with formaldehyde to give methyl methacrylate and water. Effective catalysts for the second step are, alkali metal, alkali-earth metal aluminosilicates, potassium hydroxide, lanthanum oxide and alumina.[6,7,8]

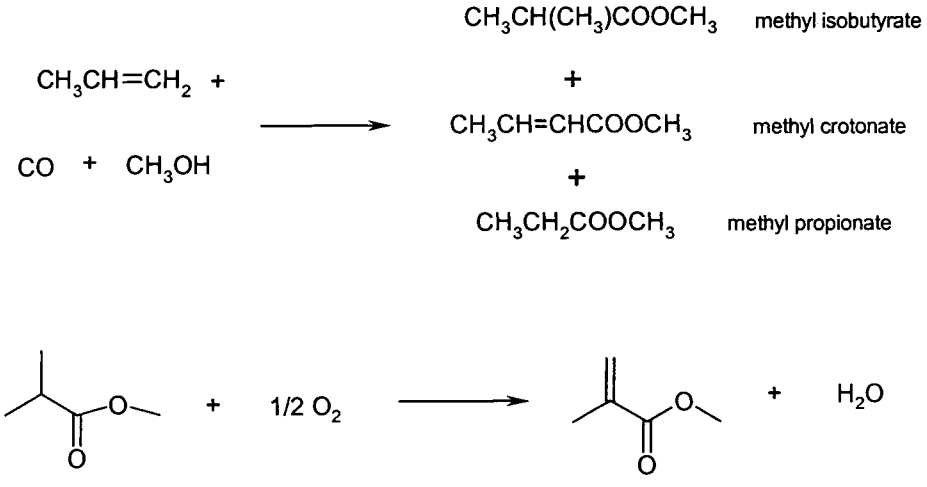
Dimethoxymethane ($CH_3OCH_2OCH_3$) is an alternative reagent to formaldehyde and is reported to give better yields and purer MMA.[9,10]



Scheme 12

2.3.2 Propylene oxycarbonylation route

Propylene reacts with carbon monoxide to give methyl isobutyrate, together with methyl crotonate and methyl propionate as side products as shown in **Scheme 13**.[11] The reaction is carried out in the liquid phase using a complex of boron trifluoride and methanol as the catalyst.

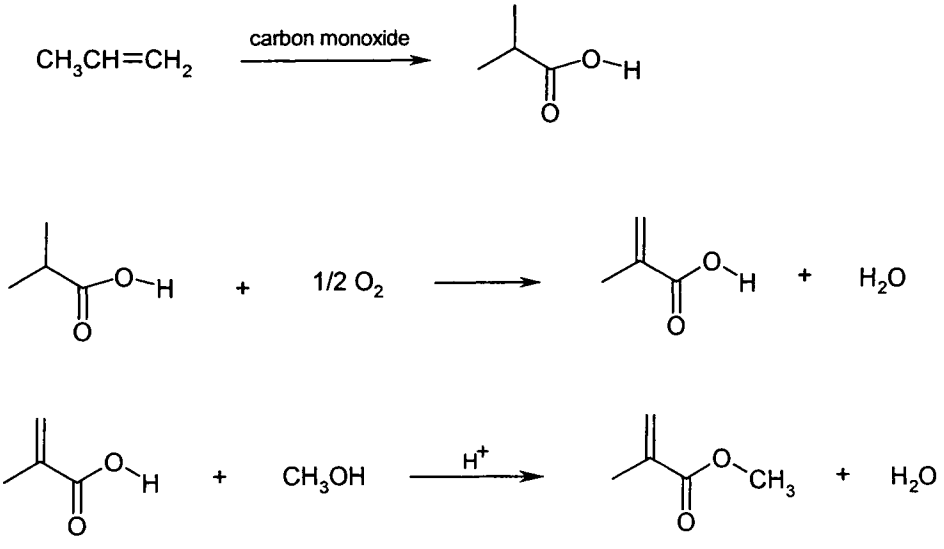


Scheme 13

Methyl isobutyrate is then 'oxydehydrogenated' in the vapour phase. There are a number of catalysts available for this second stage and these include tungsten-molybdenum[12] or molybdenum-vanadium systems[13,14] or phosphomolybdic acid with various additives.[15,16] Methyl methacrylate monomer is generally obtained in good yields of about 65-70 %.

2.3.3 The C_3 route

One of the extensively explored methods to MMA is the reaction between propylene and carbon monoxide to give isobutyric acid. The subsequent conversion to methacrylic acid followed by esterification generates methyl methacrylate as shown in **Scheme 14**. This is an attractive route because propylene and carbon monoxide are readily available starting materials.



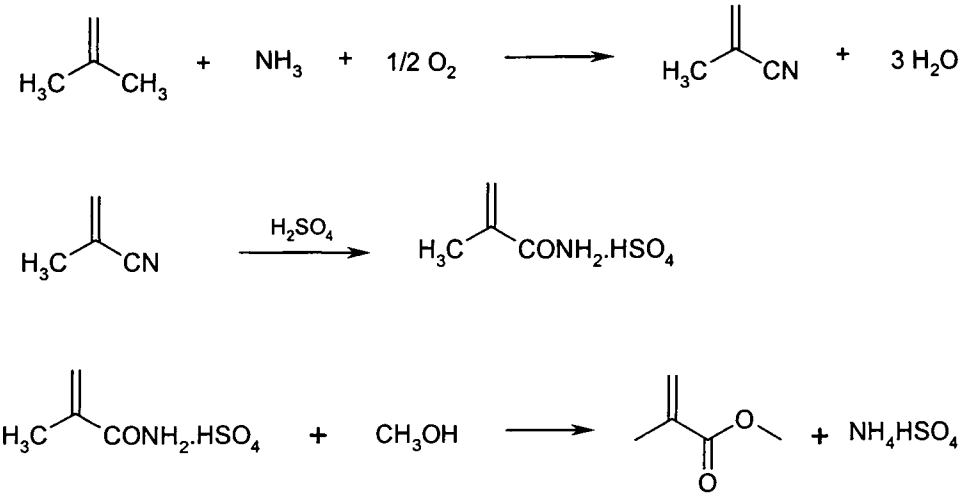
Scheme 14

In order to promote the formation of isobutyric acid in good yields, a mixture of sulphuric acid and hydrogen fluoride are used as the catalyst and the reaction medium.[17,18,19,20] Systems using boron trifluoride have also been reported as a method for the conversion of propylene to isobutyric acid.[21]

The second step of the process involves the oxidative dehydrogenation of isobutyric acid to methacrylic acid in 65-70 % yield. The methacrylic acid formed may be esterified using methanol under acidic conditions, to generate the required methyl methacrylate.

2.3.4 Methacrylonitrile route

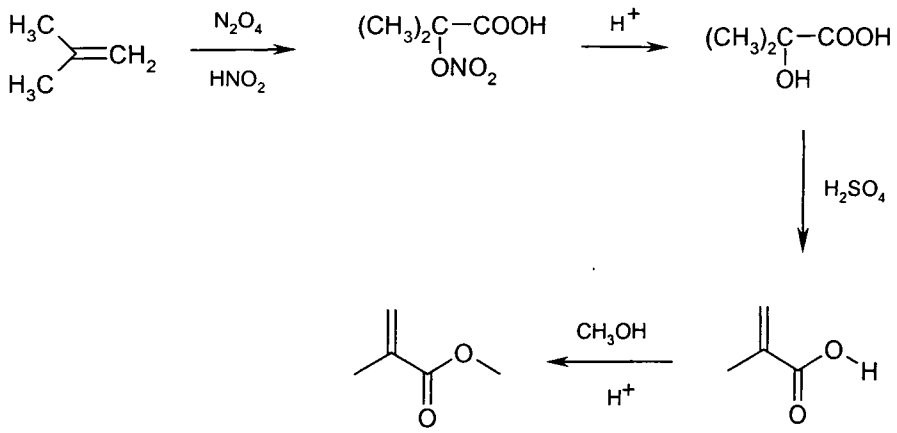
Isobutylene can be reacted with ammonia and oxygen to give methacrylonitrile. Treatment of the resultant methacrylonitrile with sulphuric acid gives methacrylamide sulphate which when treated with methanol generates methyl methacrylate. The procedure is similar to the ACP where acetone cyanohydrin is replaced by methylacrylonitrile as shown in **Scheme 15**.



Scheme 15

2.3.5 Oxidation of isobutylene

Isobutylene can be oxidised by oxides of nitrogen and nitric acid to produce nitratoisobutyric acid.[22] Acid hydrolysis of nitratoisobutyric acid leads to the formation of α-hydroxyisobutyric acid that can then be dehydrated to give the methacrylic acid. Treatment of methacrylic acid with methanol under acidic conditions produces methyl methacrylate, see **Scheme 16.**



Scheme 16

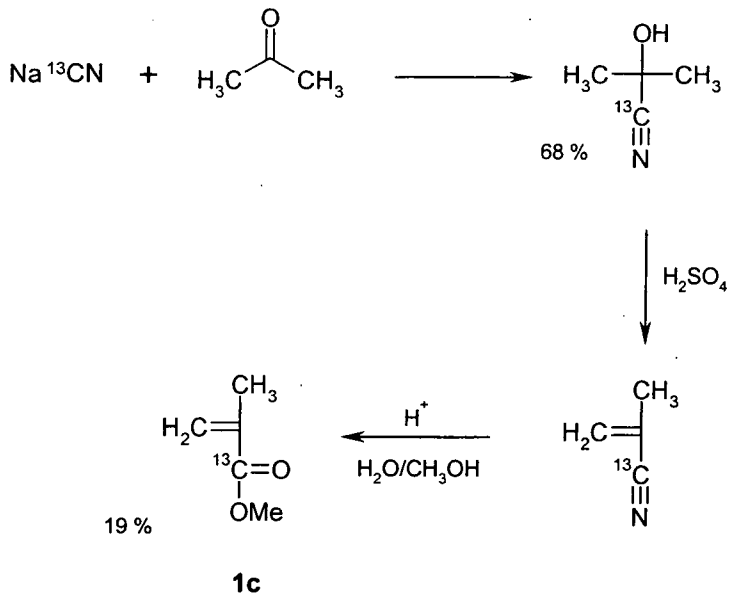
2.4 Laboratory scale routes to labelled methyl methacrylate and methacrylic acid

The routes that are discussed above for the preparation of MMA are designed for the commercial production of the monomer and their diversity reflects the scale of interest in the monomer from an industrial stand-point. Such routes are therefore generally not suitable for the laboratory scale preparation of the monomers.

With such restrictions and limitations on the processes that already exist for the preparation of MMA, various alternative laboratory scale routes suitable for the introduction of isotopic labels are reviewed. The major challenge in the preparation of MMA is in finding a suitable route that could be used to introduce the ^{13}C isotope to generate methyl [2-^{13}C]- and [3-^{13}C]-methacrylate.

2.4.1 Acetone cyanohydrin route to isotopically labelled MMA[23]

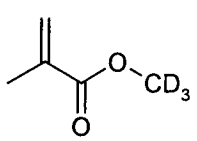
Methyl [1-^{13}C]-methacrylate **1c** has been prepared by reacting sodium [^{13}C]-cyanide and acetone, followed by treatment with sulphuric acid (40 % w/w) at 10-20 °C to give acetone cyanohydrin in a yield of 68 %. Treatment with fuming sulphuric acid results in the elimination of water to give methacrylonitrile. The esterification reaction has been carried out using acidic methanol to give methyl [1-^{13}C]-methacrylate in a very moderate yield of 19 %, see **Scheme 17**.



1c

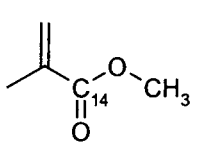
Scheme 17

In a similar manner esterification carried out using methanol-d_3 allowed the preparation of methyl [$^2H_3$]-methacrylate **1d**.[23]



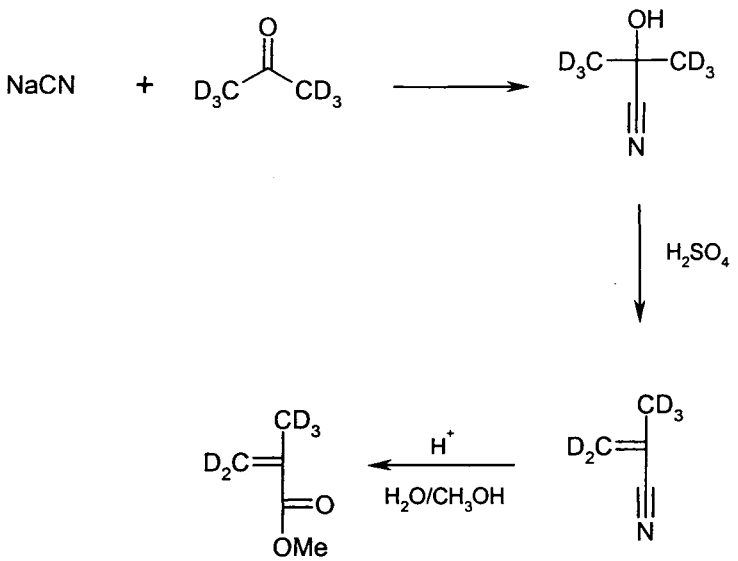
1d

This procedure has also been used to prepare methyl [1-^{14}C]-methacrylate **1e** from sodium [^{14}C]-cyanide in a 55 % yield.[24]



1e

Methyl methacrylate **1f**, carrying deuterium at the methylene and the α-methyl site has been prepared by using [$^2H_6$]-acetone cyanohydrin and methanol in the presence of sulphuric acid as shown in **Scheme 18**.[25] The initial [$^2H_6$]-acetone cyanohydrin was prepared by reacting sodium cyanide and [$^2H_6$]-acetone.

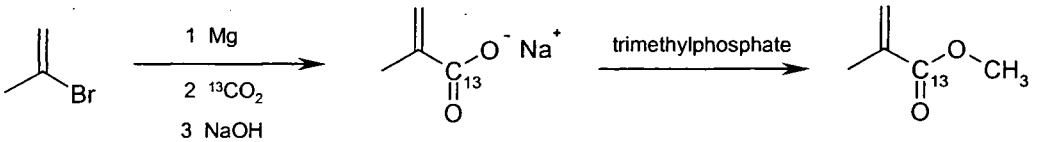


1f

Scheme 18

2.4.2 Grignard route to methyl [1-^{13}C]-methacrylate

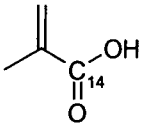
Methyl [1-^{13}C]-methacrylate **1c** has been prepared from 2-bromopropenyl magnesium bromide and $^{13}CO_2$ liberated from barium [^{13}C]-carbonate as shown in **Scheme 19**.[26] The resultant [1-^{13}C]-methacrylic acid was isolated as the sodium salt, dried at 110 °C and then converted to its corresponding methyl ester using trimethylphosphate. The reaction was carried out in the presence of hydroquinone to inhibit polymerisation. Methyl [1-^{13}C]-methacrylate was obtained in a higher yield (75-80 %) and was purer than that prepared from the acetone cyanohydrin route shown in **Scheme 17.**



1c

Scheme 19

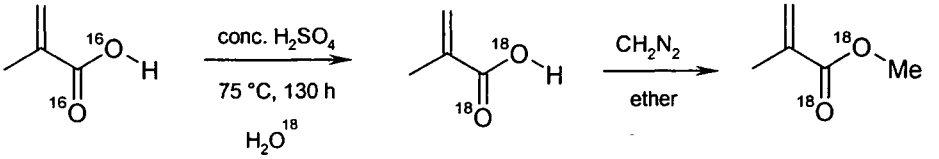
In a similar manner [1-^{14}C]-methacrylic acid **15** as been prepared using $^{14}CO_2$ liberated from barium [^{14}C]-carbonate. A yield for this reaction was not reported because the intermediate was used without isolation.[27]



15

2.4.3 Preparation of methyl [$^{18}O_2$]-methacrylate[25]

Methyl [$^{18}O_2$]-methacrylate **1g** where both oxygen atoms were enriched with ^{18}O has been prepared by the exchange reaction between methacrylic acid and ^{18}O-water as shown in **Scheme 20**. The exchange reaction was promoted by heating the mixture to 75 °C for 130 h in a sealed ampule in the presence of concentrated sulphuric acid as a catalyst and hydroquinone as polymerisation inhibitor. The resulting [$^{18}O_2$]-methacrylic acid was then converted to its corresponding methyl ester using diazomethane.

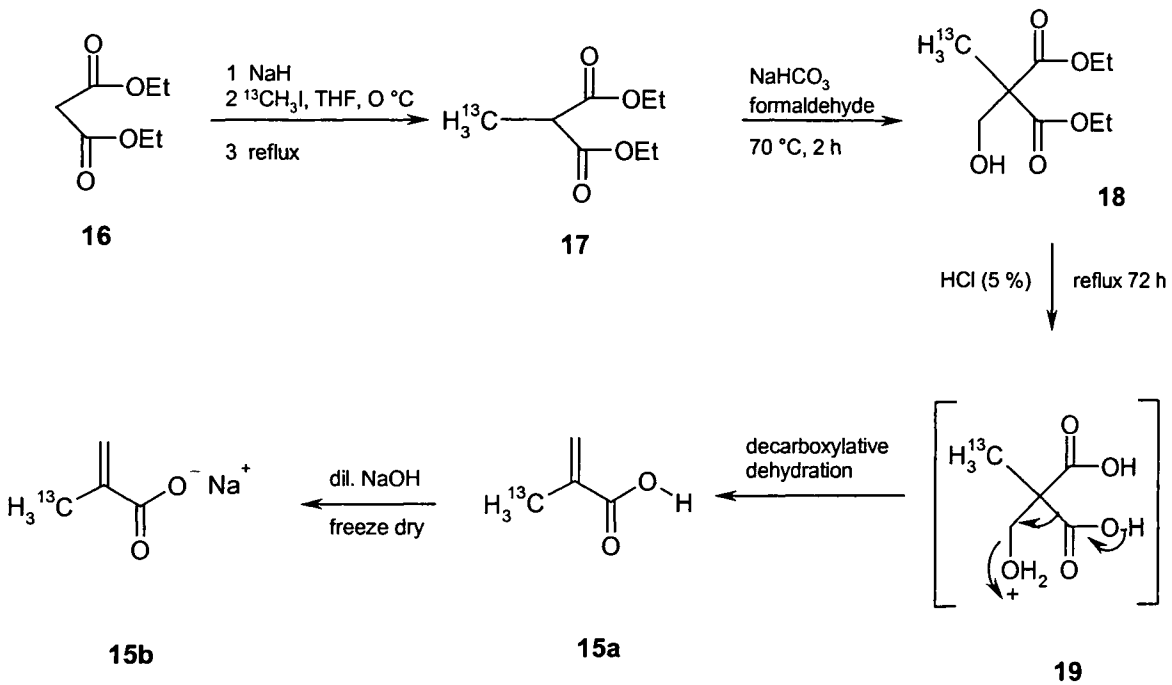


1g

Scheme 20

2.4.4 Diethyl malonate route to sodium [^{13}C-methyl]-methacrylate[28]

Sodium [^{13}C-methyl]-methacrylate **15b** has been prepared previously in Durham by methylation of diethyl malonate with [^{13}C-methyl]iodide. Reaction of the resultant diethyl [3-^{13}C-methyl]malonate **17** with formaldehyde solution in the presence of saturated sodium bicarbonate at 70°C for 2h gave diethyl (hydroxymethyl)-[3-^{13}C-methyl]malonate **18**. Treatment of this product in dilute hydrochloric acid (5 %) over 3 days, gave [3-^{13}C]-methacrylic acid **15a** *via* decarboxylative dehydration. The acid was neutralised with dilute sodium hydroxide solution and freeze dried to give sodium [3-^{13}C]-methacrylate **15b** in a 58 % yield, see **Scheme 21**.

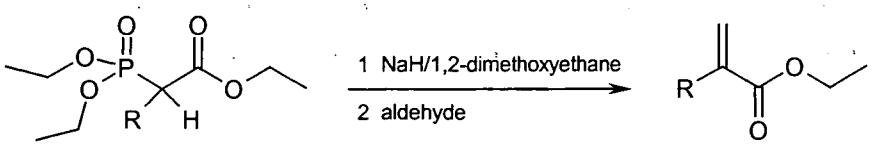


Scheme 21

2.4.5 Wittig-Horner route to MMA

Phosphonate ester anions react with aldehydes and ketones to generate olefins under relatively mild conditions.[29] The procedure is a useful supplement to the well known Wittig reaction and gives moderate to good yields of the olefin. The synthesis of olefins using phosphonates is usually cheaper in comparison to Wittig reagents and they react with a wider selection of aldehydes and ketones. Preparation of a particular substituted

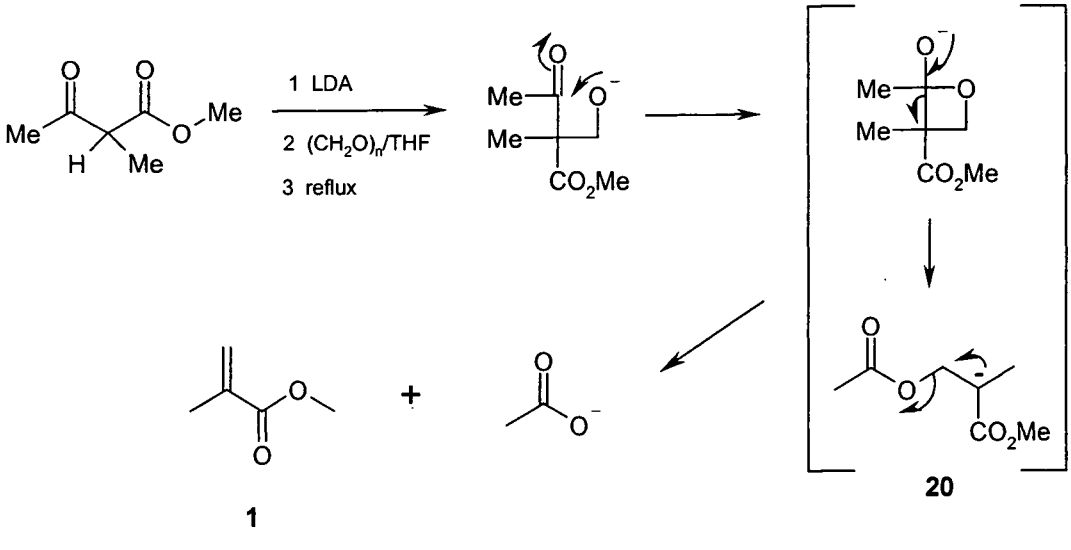
ethacrylate can be achieved by treating the appropriate phosphonate ester with sodium hydride and then reacting with an aldehyde.[30] An example of such a reaction is illustrated in **Scheme 22**.



Scheme 22

2.4.6 α-Methyl β-ketoester route to MMA

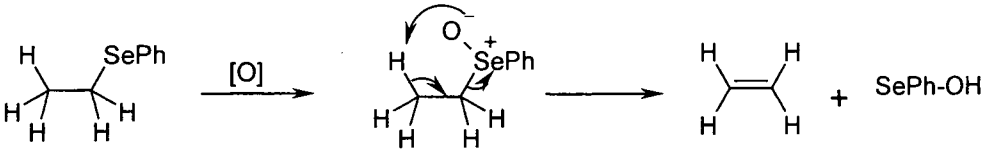
Methyl methacrylate and a number of other substituted acrylates have been synthesised from the reaction between α-monoalkylated β-ketoesters and paraformaldehyde.[31] In a typical reaction the anion was generated using LDA and was then reacted with paraformaldehyde, itself thermolysed by refluxing in THF. This process is a straightforward one pot reaction generating the product in 59 % yield and is a convenient method for the efficient preparation of methyl methacrylate. The process can be rationalised by an intramolecular acyl transfer reaction followed by elimination of acetate anion from rearranged α-carboxylate anion **20** to generate MMA as shown in **Scheme 23**.



Scheme 23

2.4.7 Selenium route to MMA

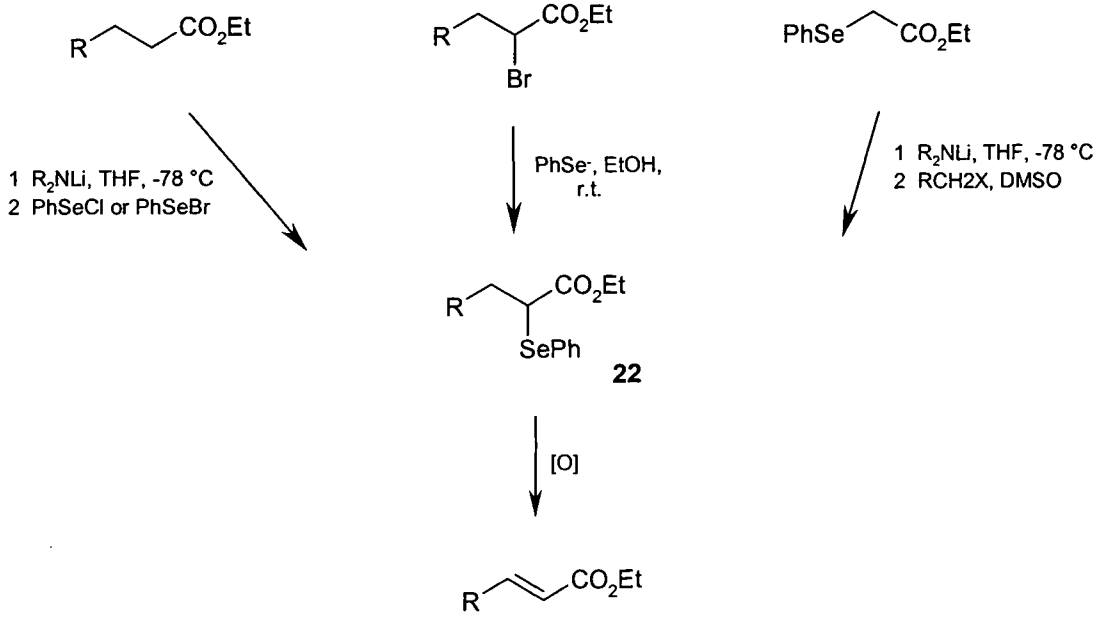
It has been known for sometime that selenoxide fragmentation, *syn* elimination processes, provide a convenient method for the introduction of unsaturation into organic frameworks.[32] Methods are well established for coupling the phenylselenide group to organic compounds for subsequent oxidation to selenoxide. Fragmentation of the selenoxide then generates the olefin **21** by a process summarised in **Scheme 24**.



21

Scheme 24

Sharpless *et al*[33] reported in 1973 that α-phenylseleno ester **22** can be oxidised to prepare α,β-unsaturated ester **23** as shown in **Scheme 25**.

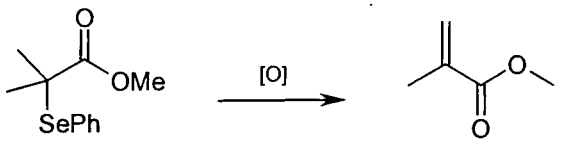


22

23

Scheme 25

By employing a similar strategy, methyl methacrylate could clearly be then prepared from methyl α-phenylselenoisobutyrate **24**. Selenoxide fragmentation would yield the required methyl methacrylate as shown in **Scheme 26**.



24 **1**

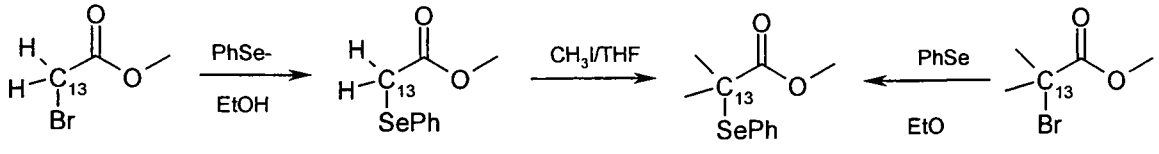
Scheme 26

2.5 Results and discussion

There are clearly a number of routes available for the preparation of isotopically labelled methyl methacrylate and recently, a route capable of introducing the ^{13}C-isotope into any position of MMA and in various combinations was reported[34]. However, this appeared in the literature at the end this research and was therefore too late to explore. Initially, a selenium route amenable for the introduction of ^{13}C-isotope was investigated.

2.5.1 Selenium route to methyl [2-^{13}C]-methacrylate

Selenoxide fragmentation introduces unsaturation into organic molecules[33] and an important intermediate for the preparation of methyl [2-^{13}C]-methacrylate in this way is methyl α-selenophenyl [2-^{13}C]-isobutyrate **24a** shown in **Scheme 27.**

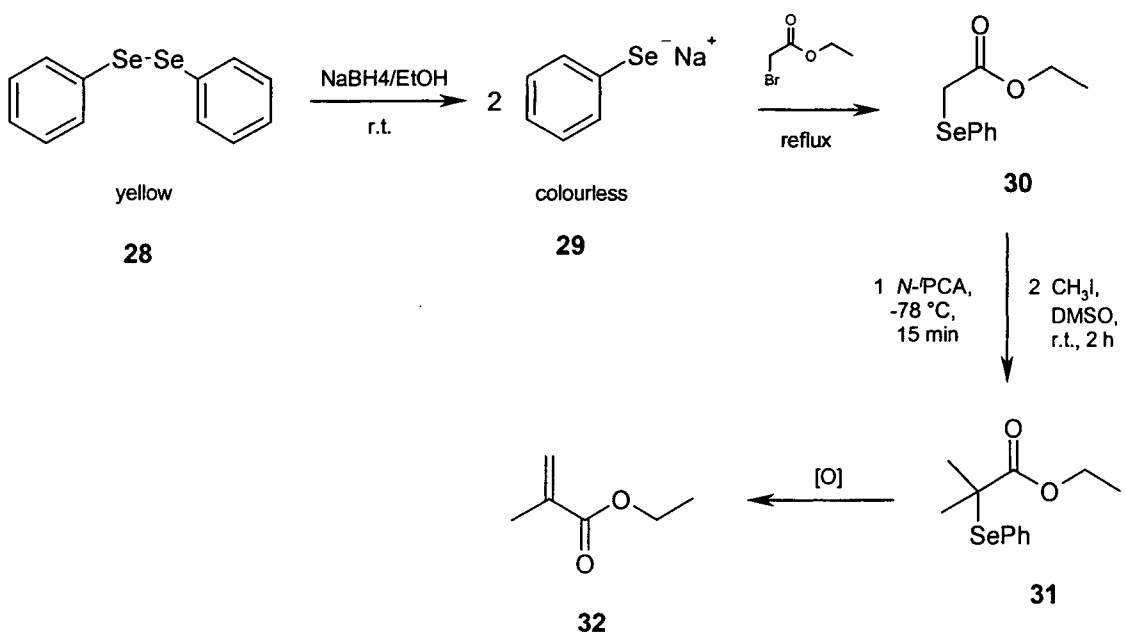


25 **26** **24a** **27**

Scheme 27

The preparation of **24a** can be approached in two ways. A reaction of methyl [2-^{13}C]-2-bromoacetate **25** and nucleophilic sodium phenylselenide ($PhSe^-Na^+$) obtained by reducing diphenyl diselenide will generate **26**. The treatment of the **26** with methyl iodide should result in the formation of methyl α-selenophenyl [2-^{13}C]-isobutyrate **24a.** Alternatively, methyl α-selenophenyl [2-^{13}C]-isobutyrate can be accessed more conveniently by reacting methyl [2-^{13}C]-2-bromoisobutyrate **27** and sodium phenyl selenide.

In the first instance a synthetic route based on ethyl [2-^{13}C]-2-bromoacetate was developed as methyl esters **25** and **27** are not available in isotopically labelled forms, see **Scheme 28**. The route was initially explored with unlabelled ethyl 2-bromoacetate to optimise each step.



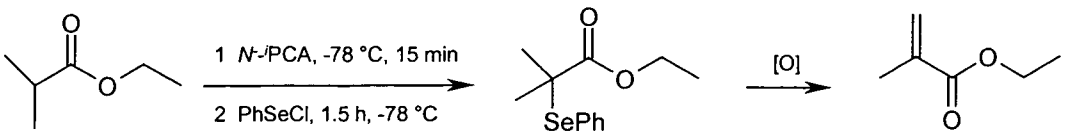
Scheme 28

The first step towards the preparation of ethyl methacrylate required reduction of diphenyl diselenide **28.** This was achieved using sodium borohydride in freshly distilled ethanol.[35] The reduction was exothermic and vigorous hydrogen evolution took place. On completion of the reaction, the bright yellow solution turned colourless indicating the formation of sodium phenylselenide. Ethyl 2-bromoacetate was then

added and the mixture heated under reflux for two hours. Purification of the crude product by distillation gave ethyl α-selenophenylacetate in a moderate yield of 50 %.[36]

The resultant ethyl α-selenophenylacetate **30** was then added to lithium *N*-isopropylcyclohexylamide (*N*-^{i}PCA) prepared by the addition of *n*-BuLi to *N*-isopropylcyclohexylamine at -78 °C.[33,37] This base has been reported to be superior to others because it is very soluble at low temperatures and 1 M solutions can be generated in THF at -78 °C. The ester enolate was then added to a solution of excess methyl iodide in DMSO. The alkylated product was recovered and then treated once again with base and methyl iodide in an attempt to secure the double alkylated product. However, it was evident after work up, from the ^{1}H-NMR spectrum, that there was a significant level of starting material together with double and mono alkylated products.

Due to the difficulties in achieving double alkylation of **30**, an alternative strategy involving the use of ethyl isobutyrate was explored, see **Scheme 29**. Deprotonation of ethyl isobutyrate followed by treatment with phenylselenium bromide or phenylselenium chloride should allow direct access to ethyl α-selenophenylisobutyrate **31**.[36] However, ethyl [2-^{13}C]-isobutyrate is not an available compound in the isotopically labelled form and a route to its preparation was therefore investigated. It has been reported that the anion of ethyl acetate can be accessed by treatment with lithium (bistrimethlysilyl)amide and then reaction with aldehydes and ketones to give excellent yields of β-hydroxy esters.[38] For optimisation of this route, it was important to establish at the outset that compound **31**, could be converted successfully to ethyl methacrylate **32**.

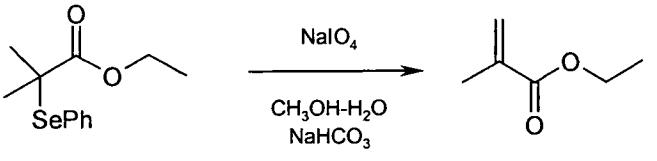


33 31 32

Scheme 29

The deprotonation to generate the enolate of ethyl isobutyrate **33** was achieved using *N*-^{i}PCA at -78 °C as described above. Phenylselenium chloride was then added and the reaction was stirred at -78 °C. After work up and purification by chromatography, ethyl α-selenophenylisobutyrate **31** was recovered in 58 % yield.

With ethyl α-selenophenylisobutyrate in hand, the compound was treated under oxidising conditions with two equivalents of peracetic acid in ethyl acetate at room temperature. It was clear from ^{1}H-NMR analysis of the resultant product that ethyl methacrylate had formed but was contaminated with several impurities. Therefore, to minimise side product formation, a milder oxidant, sodium metaperiodate, was used. The reaction in this case was carried out in the presence of sodium hydrogencarbonate in methanol as shown in **Scheme 30**.



31 **32**

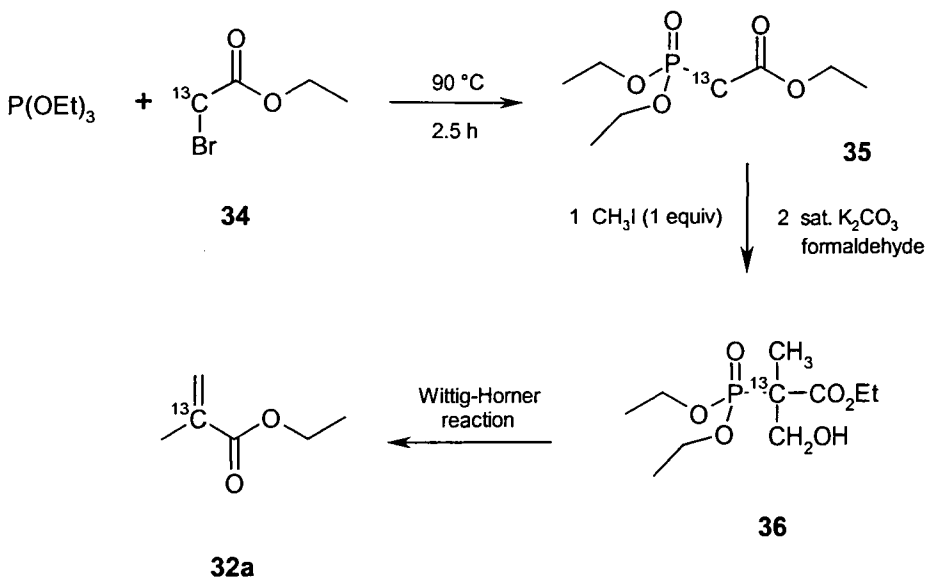
Scheme 30.

This milder reagent has been reported to give cleaner products when used in such reactions and is usually accompanied by fewer side reactions.[39] The fragmentation of the selenoxide results in the formation of mildly acidic benzeneselenic acid, pK_a = 4.79[40]. The sodium hydrogencarbonate acts to neutralise this acid as it forms and as a consequence suppress attack to the double bond. Using this method, ethyl methacrylate was obtained in a yield of 58 % after vacuum transfer.

Although this synthetic method is ideal for the preparation of ethyl methacrylate, the main disadvantage of this route is the necessity for double alkylation of ethyl acetate. It was anticipated that this may prove rather difficult and therefore, a more reliable route to methyl [2-^{13}C]-methacrylate was explored.

2.5.2 Wittig-Horner route to methyl [2-^{13}C]-methacrylate

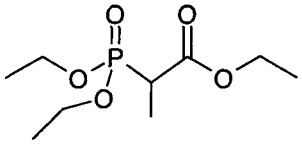
Employing a modified strategy reported by Villieras *et al*[30], methyl [2-^{13}C]-methacrylate can be prepared *via* a Wittig-Horner reaction. However, this route requires methyl [2-^{13}C]-2-bromoacetate which is not available in the labelled form whereas ethyl [2-^{13}C]-2-bromoacetate **34** is a readily available starting material. Using the latter as the starting material, the synthetic route shown in **Scheme 31** will clearly deliver ethyl [2-^{13}C]-methacrylate **32a**. It was anticipated that this ester would be a valid surrogate for MMA.



Scheme 31

Initially the route was explored with unlabelled ethyl 2-bromoacetate. This is a routine procedure in the preparation of isotopically labelled compounds to establish a reliable method to the target compound. The first step required the preparation of triethyl phosphonoacetate. This proved a relatively straightforward process and was carried out by heating ethyl 2-bromoacetate and triethyl phosphonate at 90 °C for 2.5 h. Distillation afforded a pure product, as judged by GC, in a yield of 82 %.

The next step in the route involved alkylation with methyl iodide of the resultant triethyl phosphonoacetate to prepare ethyl 2-diethylphosphonopropionate **37**.



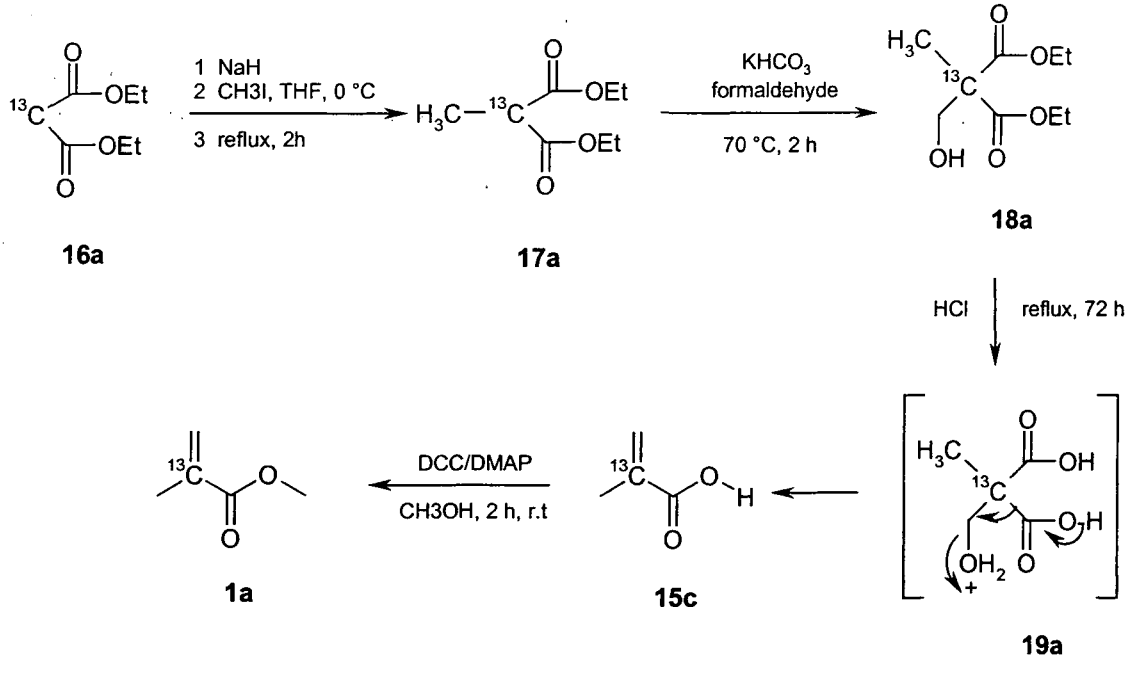
37

A number of bases, namely sodium hydride, lithium diisopropylamide and sodium ethoxide were explored to generate the triethyl phosphonoacetate anion. Methylation was carried out using methyl iodide. In each case, a mixture of starting material (~15 %), monomethylated (~65 %) and dimethylated (~20 %) was observed in the ^{1}H-NMR even when only 1 mol. equivalent of methyl iodide was added. Due to the similarities in their boiling points and polarities these compounds could not be separated by distillation or by eluting over silica gel.

Due to the difficulty in obtaining a clean sample of **37** by the above route, another route, originally developed in Durham was explored.

2.5.3 Preparation of methyl [2-^{13}C]-methacrylate *via* a diethyl malonate route

The alternative strategy the preparation of methyl [2-^{13}C]-methacrylate[28] is shown **Scheme 32**.



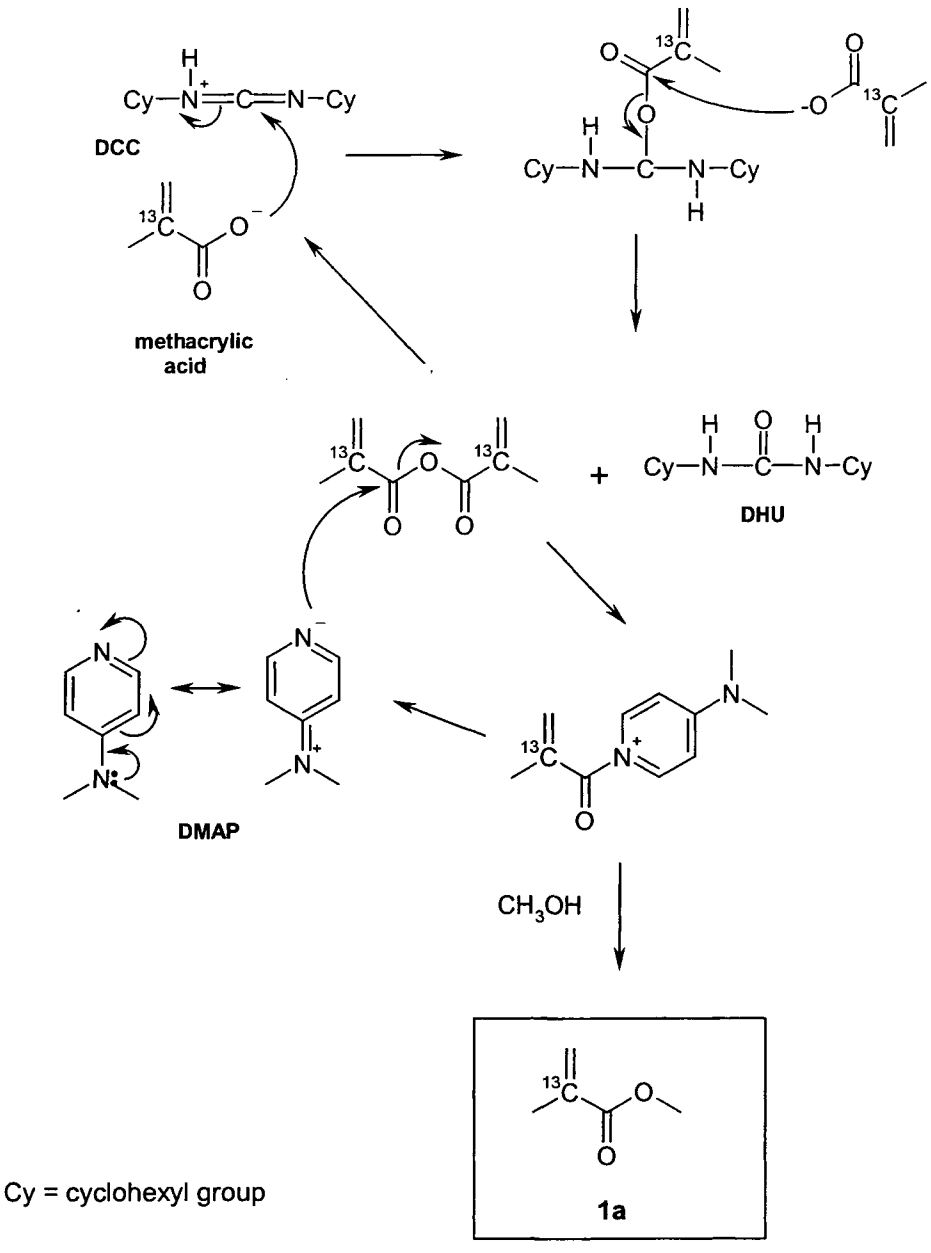
Scheme 32

The route uses diethyl [2-^{13}C]-malonate as the starting material. This is an expensive (£300/g) starting material and once again illustrates the limitations in using isotopically labelled compounds and the need to have optimised routes and high yielding steps. The route was initially explored with unlabelled diethyl malonate to establish its reliability before proceeding with labelled material.

The first step required methylation of diethyl malonate using methyl iodide in THF solution at 0 °C followed by heating to reflux. The product was isolated in an excellent yield of 90 % after extraction into diethyl ether. The ^{1}H-NMR spectrum of **17a** (unlabelled) indicated that the reaction was complete and that there was no contamination of the product from double alkylation. The diethyl methylmalonate **17a** (unlabelled) was then treated with aqueous formaldehyde followed by potassium hydrogencarbonate solution and heated to 70 °C. The resultant product diethyl

(hydroxymethyl) methylmalonate **18a** (unlabelled) was isolated (by extracting into diethyl ether) in an excellent yield of 91 %. Both the ^{1}H and ^{13}C-NMR spectra were consistent with the structure of **18a** and therefore the crude product was hydrolysed directly by heating to reflux in dilute HCl (5 %). The decarboxylative dehydration reaction was slow but was complete after 72 h generating methacrylic acid **15c**. The diethyl ether was distilled off and the methacrylic was obtained after vacuum transfer, in a yield of 95 %. It is worth noting that conventionally diethyl ether would have been removed by rotary evaporation to leave the product. However, due to the volatility of methacrylic acid under reduced pressure, this material may have been lost and was therefore was recovered by vacuum transfer.

The next step in the route was to identify a suitable reagent for the conversion of methacrylic acid to its corresponding methyl ester. This was carried out using dicylohexylcarbodiimide (DCC) in methanol with *N,N*-dimethyl aminopyridine (DMAP) as a catalyst.[41] The mechanism for the esterification process is shown in **Scheme 33**. The reaction produces dicyclohexylurea (DHU) as a precipitate and this is readily filtered from the solvent. The diethyl ether was removed by distillation and methyl methacrylate was obtained again by vacuum transfer in a moderate yield of 23 % as a clear liquid.



Scheme 33

^{1}H-NMR of the unlabelled MMA (unlabelled) prepared in this way is shown in **Figure 5**. The peak at 1.93 ppm and 3.73 ppm are of equal intensity and are assigned to the methyl and methoxy groups respectively The peaks at 5.58 ppm and 6.08 ppm are due to the vinyl CH_2 group of MMA. These are of equal intensity and clearly integrate as one proton each relative to the methyl groups.

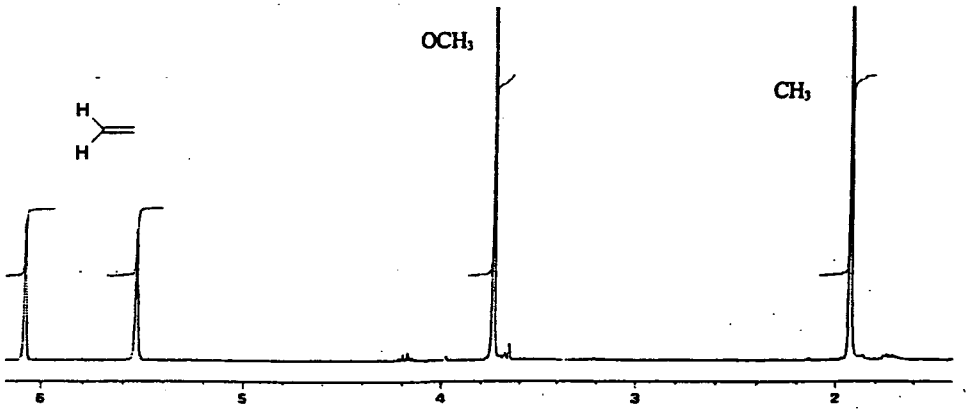


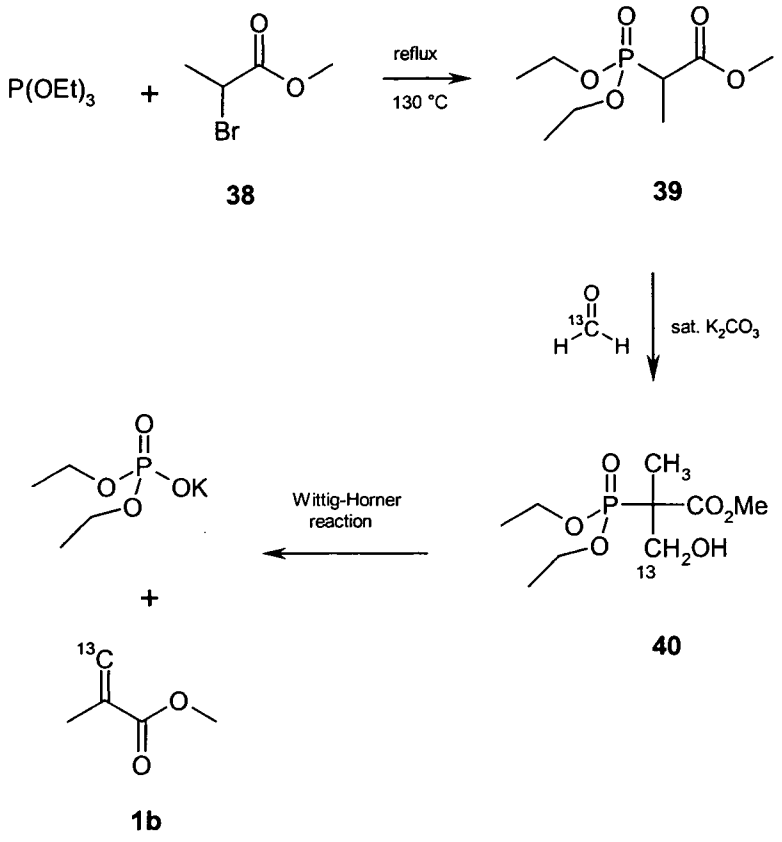
Figure 5 ^{1}H-NMR spectrum (299.9 MHz) of MMA (unlabelled) prepared *via* the methyl malonate route.

The route outlined in **Scheme 32** is a convenient and a reliable method to prepare MMA and was therefore used for the preparation of methyl [2-^{13}C]-methacrylate. From the reactions carried out to optimise this route using unlabelled diethyl malonate, it was found that the product isolated during each step was consistent with the molecular structure elucidated from MS, ^{1}H and ^{13}C-NMR spectra. In view of this and due to the expense associated with the diethyl [2-^{13}C]-malonate, the products isolated during each step of the labelled runs were not analysed as this would result in the unnecessary loss of isotopically labelled material. Using diethyl [2-^{13}C]-malonate (2 g) as the starting material, methyl [2-^{13}C]-methacrylate (282 mg) was successfully prepared. The material was used in polymerisation studies without characterisation and is discussed in Chapter 4.

2.6 Preparation of methyl [3-^{13}C]-methacrylate *via* a Wittig-Horner route

The preparation of methyl [3-^{13}C]-methacrylate proved to be a fairly straightforward process. It has already been established that substituted acrylates can be prepared using the Wittig-Horner methodology.[30]

Initially the route outlined in **Scheme 34** was optimised using unlabelled formaldehyde. The first step involved the reaction between triethyl phosphite and methyl 2-bromopropionate. When the two reagents were mixed and heated to 90 °C, the product consisted of a number of impurites (not identified). However, it was possible to generate methyl 2-(diethylphosphono)propionate **39** in a pure form by adding methyl 2-bromopropionate slowly to triethyl phosphite at 130 °C. The resultant ethyl bromide which formed as a result of the Michaelis-Arbuzov reaction was removed under reduced pressure by distillation. The reaction was complete after 16 hours of reflux and gave methyl 2-(diethylphosphono)propionate in a 70 % yield after distillation.



Scheme 34

The next step in the route is a one pot reaction to the product and involved treatment of **39** with saturated potassium carbonate solution and then reaction with formaldehyde. The MMA which was recovered by vacuum transfer was isolated in a moderate yield of 52 %. Having successfully prepared MMA *via* the route outlined in **Scheme 35**, the procedure was repeated with [^{13}C]-formaldehyde. This generated methyl [3-^{13}C]-methacrylate (290 mg) in a moderate yield of 44 % yield. The ^{1}H-NMR of methyl [3-^{13}C]-methacrylate prepared in this way is shown in **Figure 6**. The signals associated with the two vinyl protons are each a doublet observed at 5.43 ppm and 6.33 ppm with a large $^{1}J_{H\text{-}C}$ coupling constant of 106.6 Hz and 110.1 Hz respectively. The signal due to the methyl group is also a doublet and is observed at 1.95 ppm, however, with a smaller $^{3}J_{H\text{-}C}$ coupling constant of 5.8 Hz. The methoxy group is observed at 3.75 ppm as a singlet.

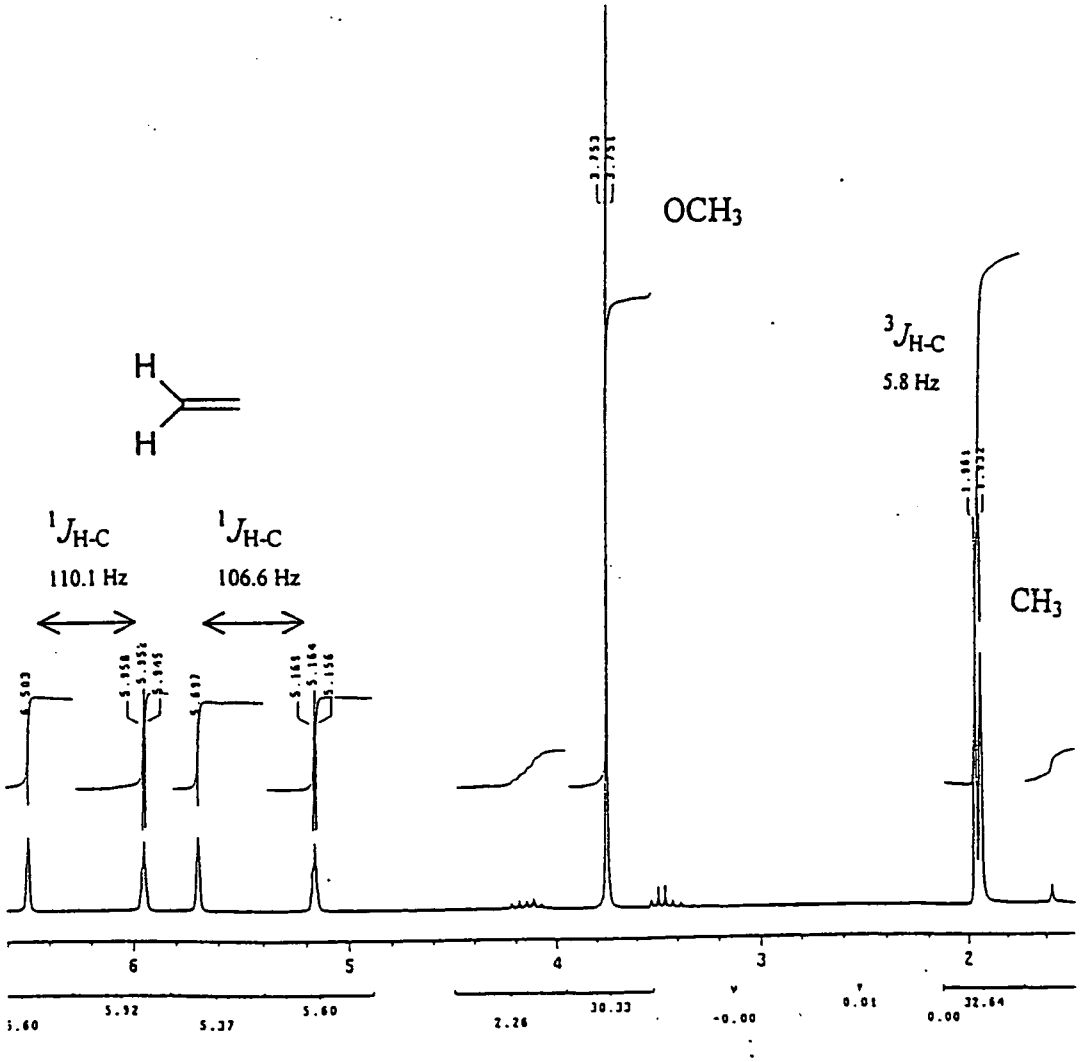


Figure 6 ^{1}H-NMR spectrum (200.0 MHz) of methyl [3-^{13}C]-methacrylate prepared.

Figure 7 shows the mass spectrum (EI) of methyl [3-^{13}C]-methacrylate. The $[M]^+$ and $[M+H]^+$ ions are observed at m/z 101 (54.8 %) and 102 (8.5 %) respectively. The peak at m/z 100 (32.4 %) is associated with the $[M]^+$-H ion.

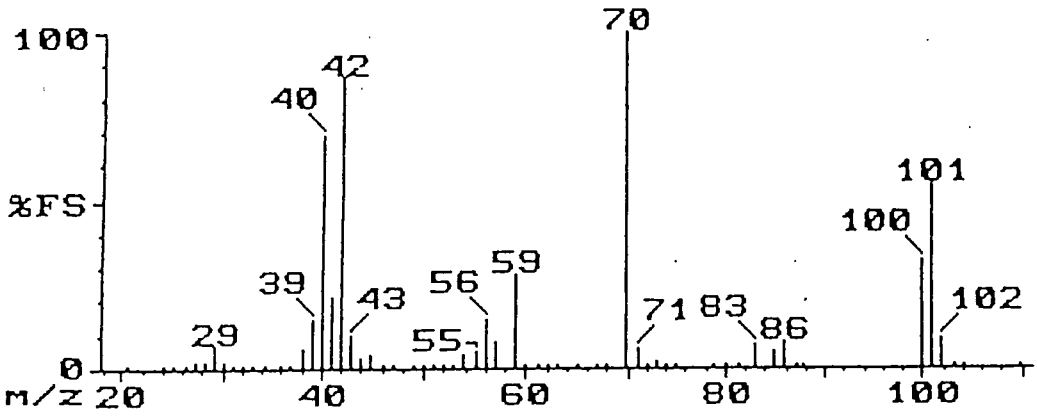


Figure 7 Mass spectrum of methyl [3-^{13}C]-methacrylate.

The methyl [3-^{13}C]-methacrylate prepared as described above was then used in polymerisation studies and is discussed in Chapter 4.

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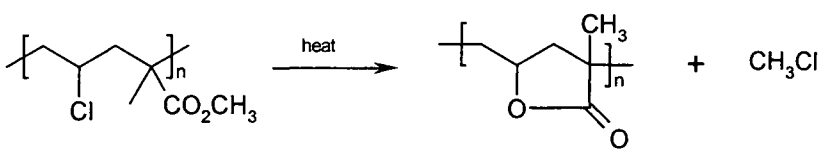
Chapter 3

Synthesis of $[^{2}H_4]$- and $[^{13}C_2]$- labelled methyl α-(hydroxymethyl) acrylate

3.1 Introduction

There is a continuous need to find materials which have superior properties and high glass transition temperatures. Polymer systems with such desirable properties are usually obtained by copolymerising suitable monomers or by introducing rigid rings into the polymer chain. In order for this new material to compete successfully with other high temperature application polymers, it must have a cost advantage, be easily processed and should have excellent weatherability. Interest in such a material originates from the increasing need to find a suitable alternative acrylic based material for lighting diffusers and car headlamps. These new applications would expand the utility of acrylics and allow it to compete more efficiently.

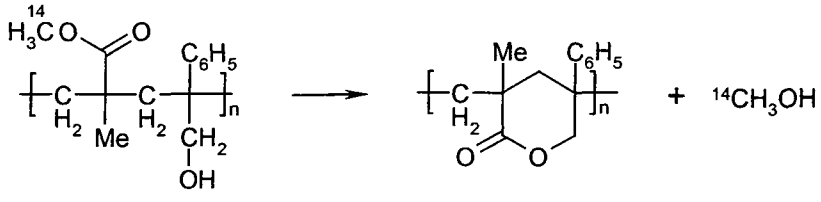
Several companies have attempted to develop polymer systems with high glass transition temperatures with attractive physical properties. In the 1960's Union Carbide explored the idea of introducing 5-membered lactone rings along the polymer backbone.[1] A copolymer of methyl methacrylate and vinyl chloride was heated to temperatures above 150 °C to give α-methyl-γ-butyrolactone groups in the polymer backbone as shown in **Scheme 35**.



Scheme 35

The viscosity of the lactonised copolymer obtained was reported to be lower than that of the untreated sample, indicating that the lactone forming reaction is intramolecular in nature. Also the lactonised copolymer had an elevated glass transition temperature as a result of chain stiffening. The elimination of chloromethane readily allowed the preparation of rigid foams with good compressive strengths. The authors reported that the lactonisation reaction is promoted by the presence of α-substituents and it was found that the ethyl acrylate copolymer did not lactonise in appreciable amounts, whereas methyl methacrylate copolymers readily formed lactones.

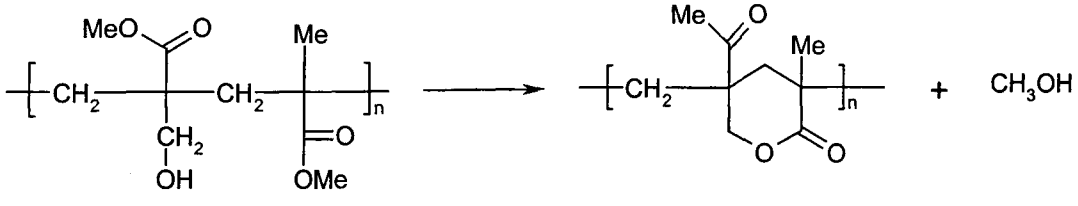
At the same time companies such as Rohm and Haas were also interested in developing polymers possessing high glass transition temperatures for high temperature applications.[2] Copolymers with various compositions of α-(hydroxymethyl)styrene and methyl methacrylate (^{14}C-labelled methyl ester) were prepared by free radical bulk polymerisation. Vacuum extrusion of the copolymer at temperatures between 400 –500 °F promoted lactone formation along the polymer backbone with release of methanol as shown in **Scheme 36**.



Scheme 36

By introducing ^{14}C-radioisotopes into the copolymer the authors reported that they were able to judge the extent of lactonisation by comparing the loss of activity of the lactonised sample to that of the calculated value for complete lactonisation. It was found that at higher compositions of α-(hydroxymethyl)styrene lactonisation was incomplete.

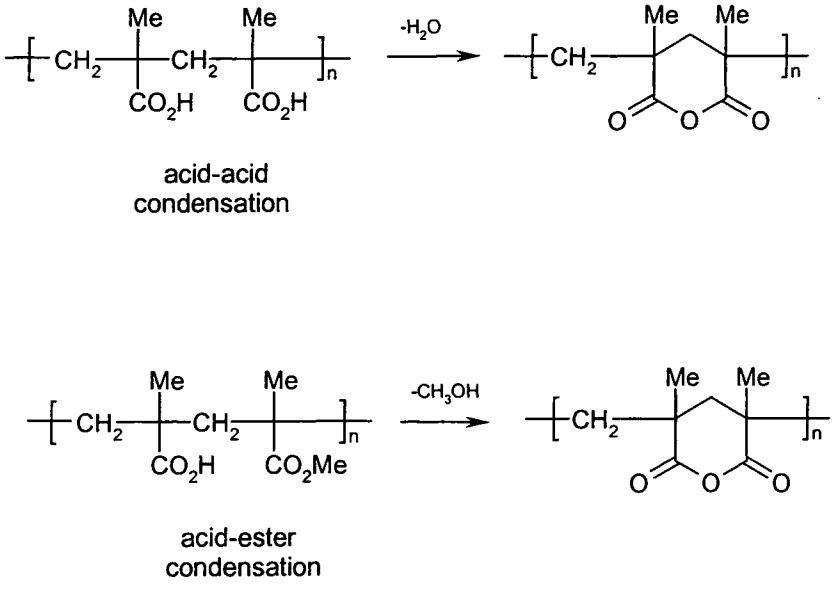
The Rohm and Haas company were also involved in extending this methodology to copolymers of methyl α-(hydroxymethyl)acrylate (MHMA) and methyl methacrylate (MMA) to introduce 6-membered lactone rings along the polymer backbone as shown in **Scheme 37**.



Scheme 37

It was reported that although the extent of lactonisation could be monitored by observing the decrease in the hydroxyl absorption in the infrared band at 3580 cm^{-1}, it was difficult to obtain quantitative values for the extent of lactonisation.[2]

There has been a long interest in introducing rigid intramolecular ring structures into the polymer backbone. During the 1980's, Ineos Acrylics (formally, ICI Acrylics) explored the idea of introducing anhydride rings into the polymer chain. This was carried out by reactive vented extrusion (where the volatile gases were removed) of either the methacrylic acid polymer or the methyl methacrylate/methacrylic acid copolymer, see **Scheme 38**.

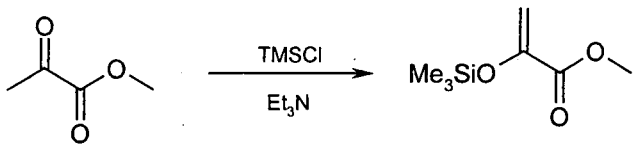


Scheme 38

The cyclisation reaction results in the formation of a poly(glutaric anhydride) and depending on copolymer composition, these materials have glass transistion temperatures between 130-150 °C. However, because of the poor weatherability of poly(glutaric anhydride), a search for alternative materials was initiated.

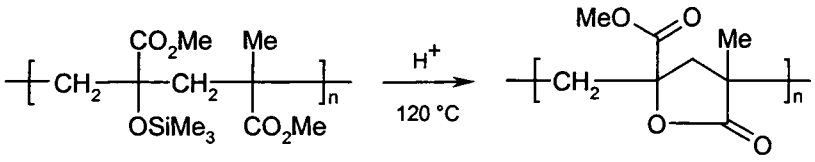
Other attempts to generate polymers with high glass transition temperatures included introducing 5-membered lactones into PMMA e.g. by using methyl 2-

(trimethylsiloxy)acrylate as a monomer. This monomer was prepared in a relatively straightforward manner by reacting methyl pyruvate with trimethylsilylchloride, in the presence of triethylamine as shown in **Scheme 39**.



Scheme 39

Methyl 2-(trimethylsiloxy)acrylate was then copolymerised with methyl methacrylate and extruded at 120 °C under acidic conditions to promote lactone formation as shown in **Scheme 40**.



Scheme 40

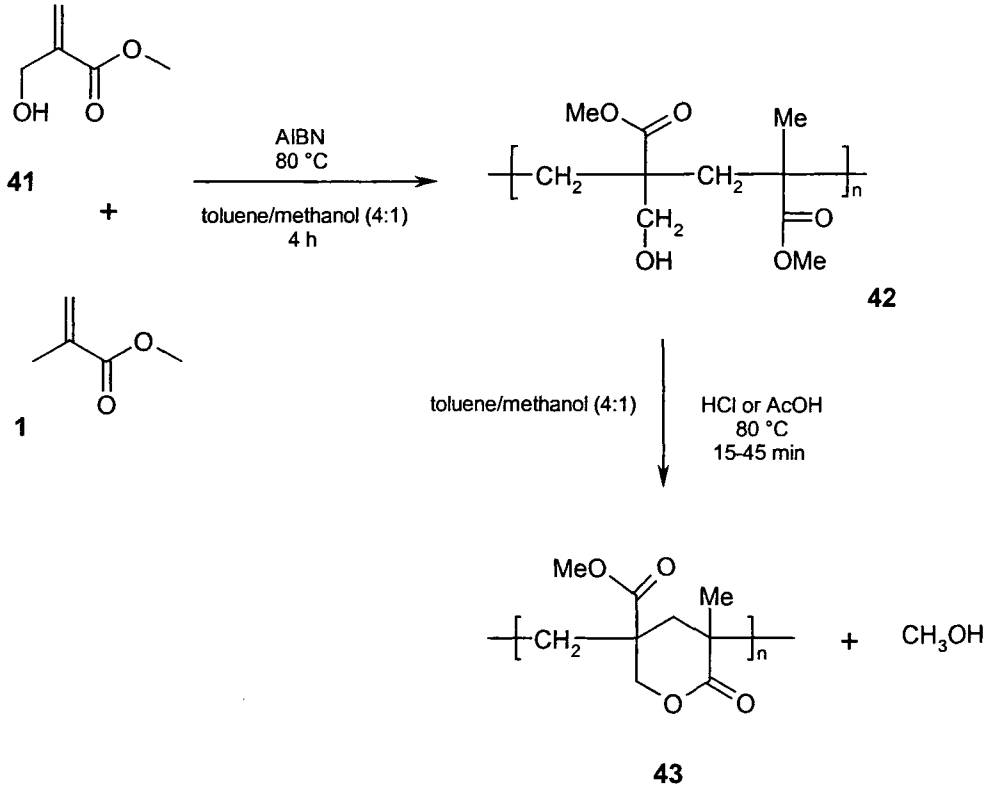
The resultant lactonised PMMA had a *Tg* of 157 °C at 27 mol.% of methyl 2-(trimethylsiloxy)acrylate. Although these physical properties were encouraging, attempts to commercialise the product were discontinued due to the high costs associated with the synthesis of methyl 2-(trimethylsiloxy)acrylate.

The weatherability of the lactonised polymers depend on the level of unreacted hydroxyl groups which are associated with rapid water absorption. Therefore, to commercialise lactonised methyl methacrylate and methyl α-(hydroxymethyl)acrylate copolymer, the route originally reported by Rohm and Haas (discussed above) needed optimising. In order to overcome incomplete lactonisation two approaches were proposed.

(i) Identify a suitable catalyst that would efficiently promote ring closure in excess of 99 % in a reactive extrusion process.

(ii) Identify a reagent which, when added in the final stages of the reactive extrusion, would react with any residual hydroxymethyl groups.

Having identified procedures to overcome incomplete lactonisation of the copolymer, laboratory scale trials to prepare the copolymer of methyl methacrylate **1** and methyl α-(hydroxymethyl)acrylate **41** by free radical methods began in the early 1990's, see **Scheme 41**. Initially, all of the copolymerisations were carried out in a toluene/methanol (4:1) solution at 80 °C over a duration of 4 hours. The lactonisation reaction was carried out *in-situ* and it was found that it proceeded with ease when small amounts of concentrated hydrochloric acid or acetic acid were added and heated to 80 ° C for 15-45 minutes. In some cases the copolymer was isolated and then lactonised in a solution of toluene/methanol under similar conditions.



Scheme 41

The *Tg* of the lactonised copolymer change with different mole % concentrations of methyl α-(hydroxymethyl)acrylate. At compositions of typically 40 mole %, a *Tg* of 165 °C is achieved, whereas lower concentrations of about 25 mole % gives a material with a *Tg* of 135 °C.

Following the successful preparation of the lactonised copolymer by solution methods, attention focused on generating the material using a twin extruder. However, a suitable catalyst was needed and from the laboratory scale solution lactonisation trials it was discovered that lactonisation proceeded most efficiently under acid catalysis. Therefore, extrusion trials were conducted at 220 °C using *p*- toluene sulphonic acid as the catalyst. The samples were analysed by FT-IR and the extent of lactonisation was judged by the decrease in intensity of the peak associated with the broad hydroxyl peak at 3500 cm^{-1}. In copolymers prepared with 20 mol.% of methyl α-(hydroxymethyl)acrylate it was found that complete lactonisation had taken place, whereas at higher levels, full lactonisation proved more difficult to achieve with a single pass through the extruder. Although FT-IR gave a reasonable indication of lactone content in the copolymer, it was by no means an absolute method to quantify the presence of any unreacted hydroxyl groups in the lactonised copolymer.

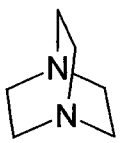
In view of this, it became important to evaluate the degree of lactonisation by ^{13}C-NMR. The progress of the lactonisation reaction could be monitored by observing the change in the chemical shift of the CH_2OH group from 52 to 60 ppm as it was converted to the lactone. However, the sensitivity of this analytical method is limited as it relies on only 1.1 % natural abundance of ^{13}C. In order to improve this analysis, introduction of ^{13}C and ^{2}H isotopes into methyl α-(hydroxymethyl)acrylate **41** was addressed.

3.2 Review of the methods available for the preparation of methyl α-(hydroxymethyl)acrylate

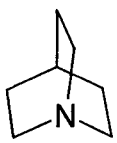
In designing an approach to the synthesis of methyl α-(hydroxymethyl)acrylate, a route was required which was amenable to the introduction of the isotope. There are only a few reliable routes to this monomer and these are reviewed below.

3.2.1 Baylis-Hillman reaction

The α-position of activated alkenes, under the influence of a tertiary amine catalyst undergo reaction with carbon electrophiles resulting in α-hydroxy functionised molecules. Baylis and Hillman originally reported three catalysts which are, diazobicyclo[2.2.2] octane (DABCO) **44**, quinuclidine **45** and pyrrocoline **46**.[3]



44



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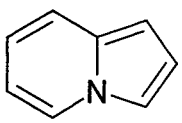
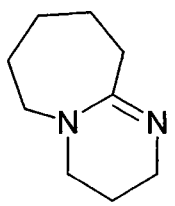


46

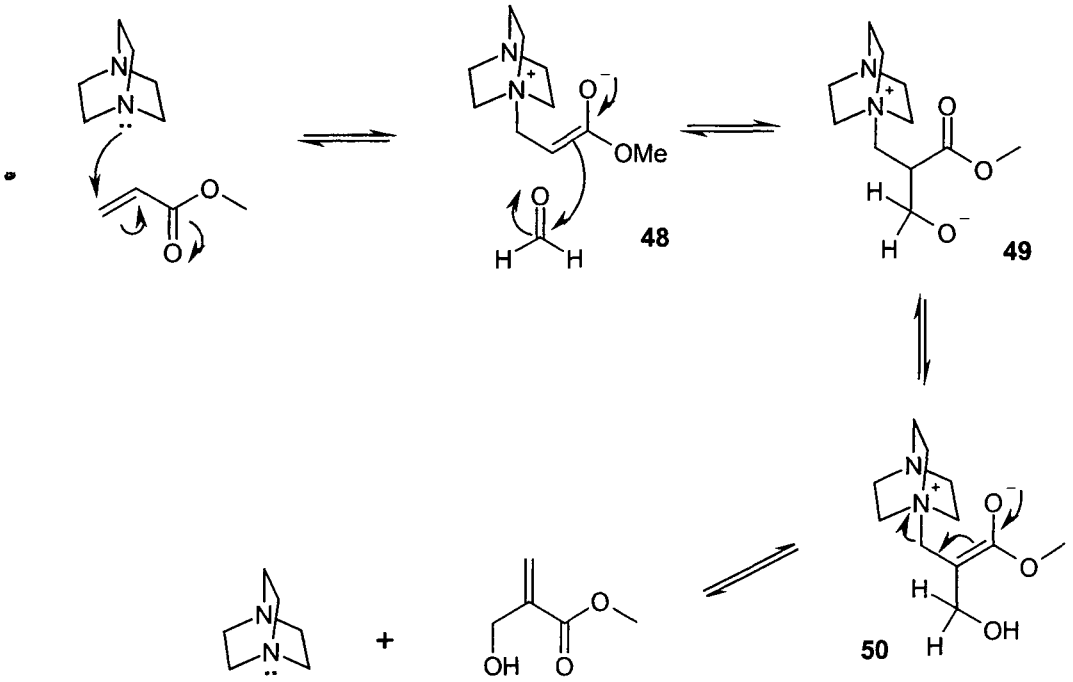
However, in a recent publication[4] (October 99), it was reported that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **47** catalysed Baylis-Hillman reactions were faster and gave cleaner products.



47

Numerous activated alkenes such as acrylic esters, acrylonitrile, vinyl ketones, phenyl vinylsulphone, vinyl phosphonate, allenic acid ester and acrolein have been reacted with a variety of electrophilic reagents such as aliphatic, aromatic and hetro aromatic aldehydes, α,β-unsaturated aldehydes, paraformaldehyde or formalin and functionlised aldehydes.[5] Activated alkenes also readily react with α-keto esters and fluorinated ketones. Ketones, however, generally do not undergo the Baylis-Hillman reaction under the usual conditions and therefore elevated pressures and specific catalysts are usually required for their successful reaction.

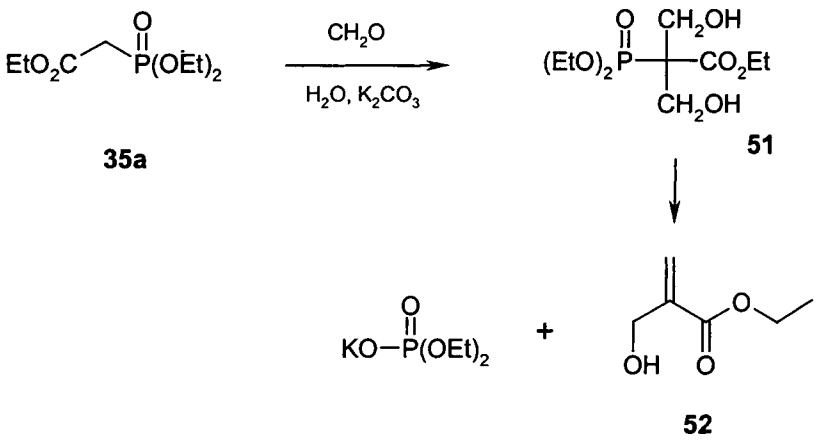
Methyl α-(hydroxymethyl)acrylate has been prepared in a moderate yield (27 %) by heating methyl acrylate and paraformaldehyde in the presence of DABCO as the catalyst[6], **Scheme 42**. The reaction is initiated by a Michael type nucleophilic attack by DABCO onto the methyl acrylate. Formaldehyde is then subjected to nucleophilic attack from the transient zwitter-ionic enolate **48**. The resultant dipolar adduct **49** then undergoes proton migration followed by elimination of DABCO to give methyl α-(hydroxymethyl)acrylate.



Scheme 42

3.2.2 Wittig-Horner reaction

The Wittig-Horner route has been used for the preparation of ethyl α-(hydroxymethyl)acrylate in good yields. This is achieved by reacting triethyl phosphonoacetate **35a** and aqueous formaldehyde solution as shown in **Scheme 43**.[7,8] Potassium carbonate is generally used to generate the anion of triethyl phosphonoacetate which readily reacts with formaldehyde in a Wittig-Horner type reaction. Ethyl α-(hydroxymethyl)acrylate is also obtained by using paraformaldehyde in place of aqueous formaldehyde solution. The paraformaldehyde is depolymerised by heating in phosphoric acid solution before it was treated with triethyl phosphonoacetate.[8] However, if this route is to be used for the preparation of methyl α-(hydroxymethyl)acrylate, then methyl 2-(diethylphosphono)propionate is required.



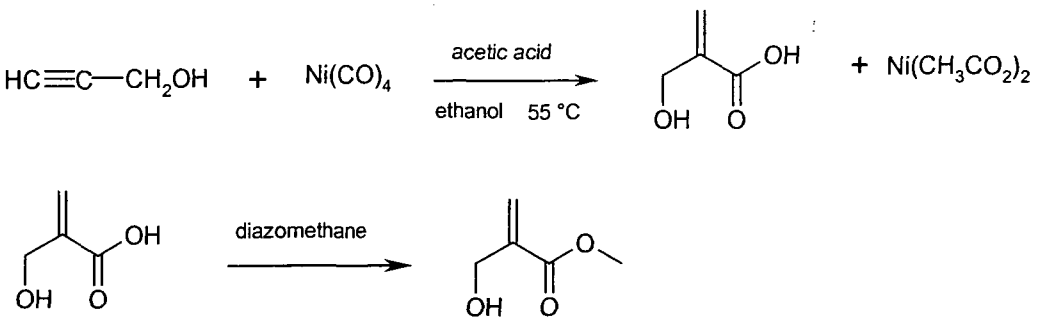
35a **51** **52**

Scheme 43

3.2.3 A route from propargyl alcohol[9]

Nickel carbonyl can be used to catalyse the reaction between propargyl alcohol and acetic acid in ethanol to give α-(hydroxymethyl)acrylic acid albeit in a poor yield (18 %), see **Scheme 44**. The resultant α-(hydroxymethyl)acrylic acid prepared was then purified to remove any traces of nickel and converted to its methyl ester by treatment with diazomethane. The product methyl α-(hydroxymethyl)acrylate prepared in this

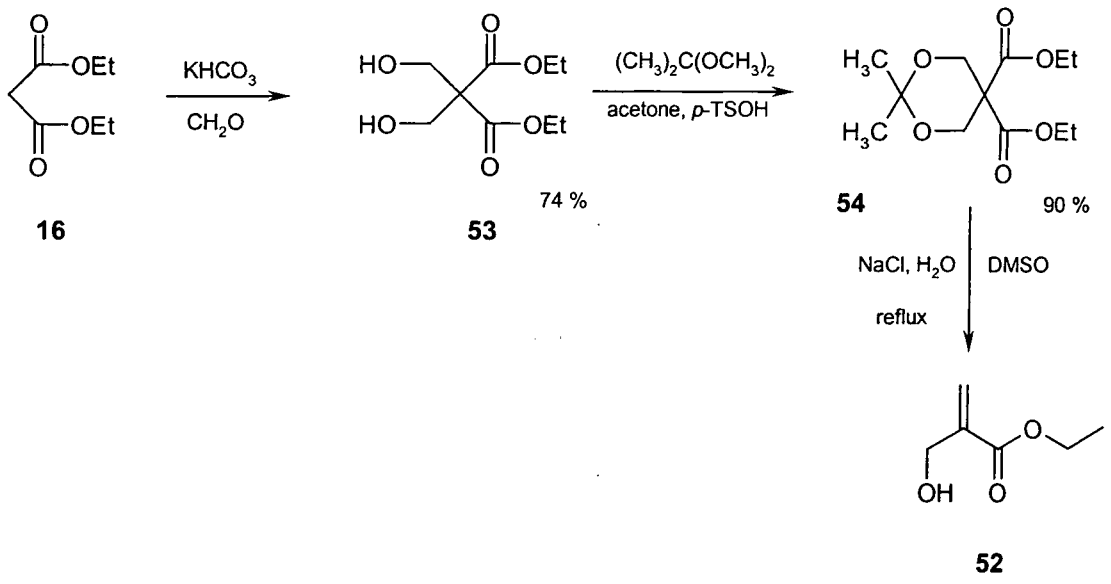
way was reported to have been obtained in a yield of 34 %, however, it was contaminated with several impurities, presumably from diazomethane addition to the double bond.



Scheme 44

3.2.4 Diethyl malonate route[10]

Ethyl α-(hydroxymethyl)acrylate was obtained as a major side product of this particular synthetic route which first involved treating diethyl malonate **16** with formaldehyde solution using potassium hydrogencarbonate as the base, see **Scheme 45**. The resulting diethyl bis(hydroxymethyl)malonate **53** was treated with *p*-toluene sulphonic acid and 2,2-dimethoxypropane in acetone to give 2,2-dimethyl-5,5-dicarbethoxy-1,3-dioxane **54**. The resultant product was then refluxed in sodium chloride solution containing dimethyl sulphoxide to generate ethyl α-(hydroxymethyl)acrylate. It was noted that the yield of the side product increased when sodium chloride solution was replaced with lithium chloride. No yield for the formation of ethyl α-(hydroxymethyl)acrylate was reported.[10]

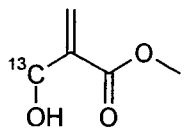


16 **53** **54** **52**

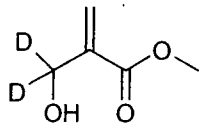
Scheme 45

3.3 Aims and objectives

Preparation of ^{13}C and ^{2}H isotopically labelled methyl α-(hydroxymethyl)acrylate became a key objective of this project in order to evaluate the extent of lactonisation in copolymers generated from MMA. Due to the low natural abundance of the ^{13}C isotope (1.1 %), low intensity signals from unreacted hydroxymethyl groups are difficult to detect in the ^{13}C-NMR without ^{13}C enrichment. Similarly, by introducing the ^{2}H isotope which is present at a natural abundance of 0.015 % into methyl α-(hydroxymethyl)acrylate, signals from unreacted hydroxymethyl groups will be enhanced in the ^{2}H-NMR of the lactonised copolymer with MMA. In view of this, the preparation of methyl α-(hydroxymethyl)acrylates **41a** and **41b** became the objective.

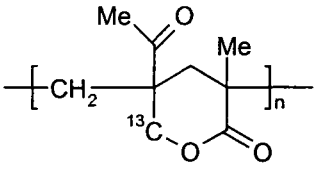


methyl [α-^{13}C]-(hydroxymethyl)acrylate **41a**

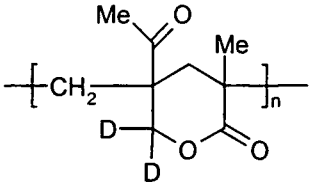


methyl [α-$^2H_2$]-(hydroxymethyl)acrylate **41b**

The incorporation of isotopic labels into the hydroxymethyl group should clearly enhance the low intensity signals of any unreacted CH_2OH groups carrying the isotope, thereby enabling easier detection of such groups in the resultant lactonised copolymer **43a** and **43b** by ^{13}C and ^2H-NMR respectively



[^{13}C]-labelled lactone **43a**



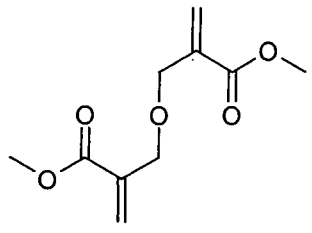
[$^2H_2$]-labelled lactone **43b**

3.4 Results and discussion

There are a only a few reliable routes available for the preparation of methyl α-(hydroxymethyl)acrylate. The Baylis-Hillman reaction has recently received much attention for the straightforward preparation of α-functionalised acrylates. The major drawback, however, is the time taken for the reaction to reach completion. We were interested in exploring the Baylis-Hillman reaction particularly because it presented a convenient route for the introduction of the ^{13}C or ^2H isotopes into the desired position of the monomer, by using either [^{13}C]- or [$^2H_2$]-formaldehyde.

Initial attempts aimed at the preparation of methyl α-(hydroxymethyl)acrylate were carried out by reacting methyl acrylate (1 equiv.) and unlabelled formaldehyde solution (1 equiv.) with a catalytic amount of DABCO (1 equiv.) over a duration of 50 h. After work up, the product was analysed by ^1H-NMR and GC. It was clear that there were several impurities present in the crude product. From the ^1H-NMR it was evident that

the major constituent, accounting for greater than 36 % of the crude product, was the dimerised methyl α-(hydroxymethyl)acrylate ether **55** and this was consistent with the structure elucidated by Drews *et al.*[10] Methyl α-(hydroxymethyl)acrylate present in the crude product was estimated to be no greater than about 5-8 % in total.



55

It became apparent that the method needed optimisation. Many authors have reported that the use of aqueous formaldehyde leads to side reactions and contamination of the product and have recommended paraformaldehyde as an alternative reagent.[11] In a typical experiment, methyl acrylate, paraformaldehyde and DABCO were reacted for several hours at room and at elevated temperatures, see **Table 10**. After work up of the reaction mixture, the ^{1}H-NMR analysis revealed that most of this material was unreacted methyl acrylate.

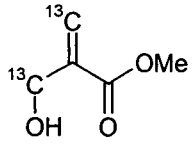
Methyl acrylate (mol. %)	Paraformaldehyde (mol. %)	DABCO (mol %)	Temperature (°C)	Duration (h)	Yield (%)
1	1.5	0.05	95	4	< 2
1	1.5	0.05	25	72	<5
1	1.5	1	25	72	<1

Table 10 Reaction conditions for the DABCO catalysed route to methyl α-(hydroxymethyl)acrylate.

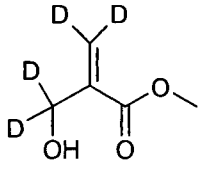
Finally, a further reaction was carried out in a polar reaction medium as there is evidence that the rate of the Baylis-Hillman reaction is somewhat enhanced in a polar medium.[12,13] Using THF as the solvent, a reaction mixture comprising of methyl acrylate, formaldehyde solution and DABCO (4:1:1) was stirred for 48 h. After work up the crude product was analysed by ^{1}H-NMR, however, there was no evidence for the presence of methyl α-(hydroxymethyl)acrylate. In view of this an alternative method for the preparation of methyl α-(hydroxymethyl)acrylate was explored.

3.5 Preparation of isotopically labelled methyl α-(hydroxymethyl)acrylate (MHMA) *via* a Wittig-Horner route

Having attempted and failed several times to prepare methyl α-(hydroxymethyl)acrylate by the Baylis-Hillman reaction, our attention turned to the Wittig-Horner route.[7] This route would allow the preparation of methyl α-(hydroxymethyl)acrylate labelled with either ^{13}C or ^{2}H isotope in two positions.



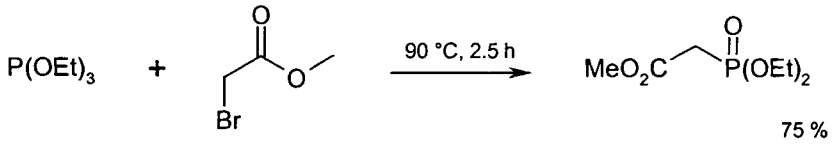
methyl [α-^{13}C]-(hydroxymethyl)-[3-^{13}C]-acrylate **41c**



methyl [α-$^{2}H_2$]-(hydroxymethyl)-[3-$^{2}H_2$]-acrylate **41d**

Preparation of isotopically labelled methyl α-(hydroxymethyl)acrylate *via* a Wittig-Horner reaction requires the phosphonate **56** as a starting material and this was prepared by reacting triethyl phosphite and 2-bromomethyl acetate *via* a Michaelis-Arbuzov type

reaction as shown in **Scheme 46**. This was a straightforward process and the material was obtained as a clear liquid in a good yield of 75 %. This material was judged to be pure (>99 %) by GC analysis and was used without further purification.



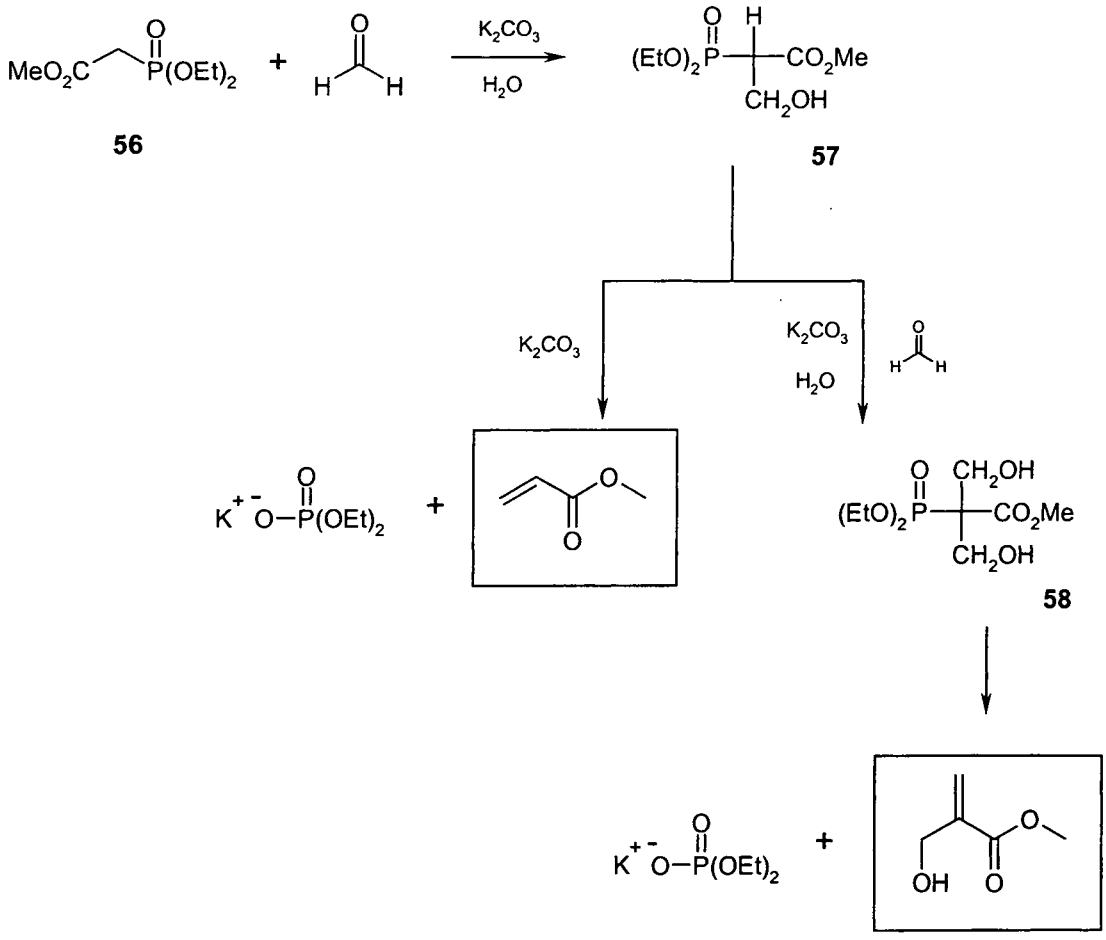
75 %

56

Scheme 46

Having successfully generated **56,** the next step in the route was to optimise the reaction with 20 wt.% aqueous formaldehyde solution as both the [^{13}C]-and [$^{2}H_2$]-formaldehyde solutions are supplied at this concentration. Therefore, the commercially supplied aqueous formaldehyde solution which is at a concentration of 36 wt.% was diluted appropriately.

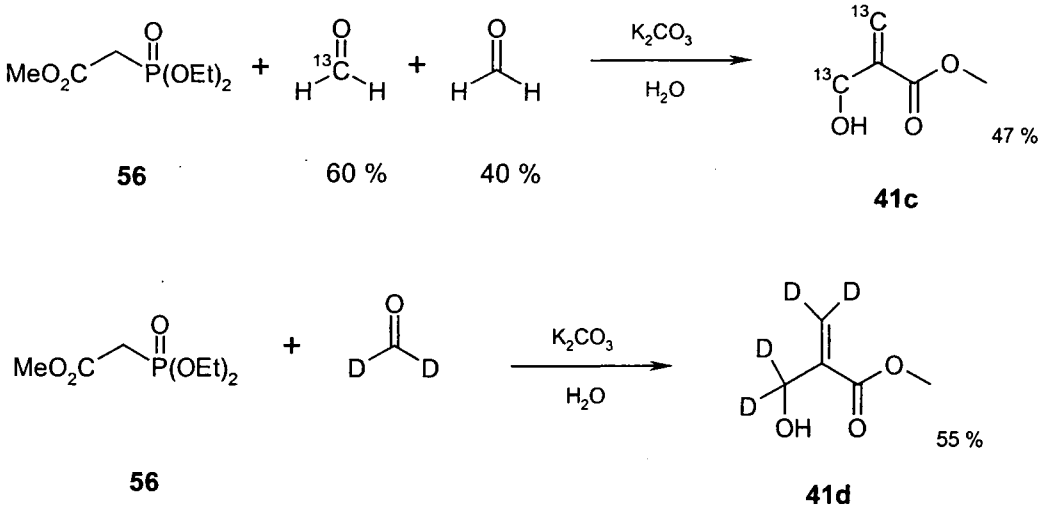
Two equivalents of 20 wt.% formaldehyde solution were added to the phosphonate **56** and the reaction stirred until the solution was homogeneous. In order to generate the anion of **56**, saturated potassium carbonate solution was added slowly to the reaction. After work up, the ^{1}H-NMR of the crude product revealed much of this was in fact methyl acrylate. The drawback of the Wittig-Horner route is that it suffers from a competing elimination reaction that results in the formation of methyl acrylate, see **Scheme 47**



Scheme 47

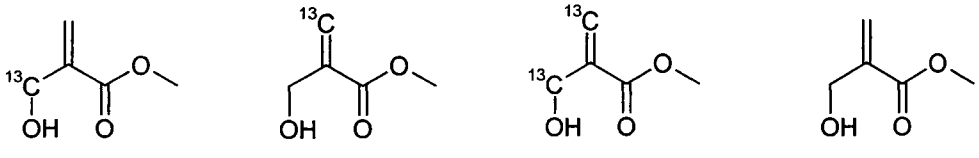
This problem was overcome[7] by using an excess of formaldehyde solution. Thus when four equivalents of 20 % formadehyde solution were used, the competing elimination reaction was not observed. Eluting the isolated crude product over silca gel gave methyl α-(hydroxymethyl)acrylate in a moderate yield (50 %).

Despite the modest yield, clean material, as judged by GC analysis, was recovered. The next objective was to prepare the labelled targets using [^{13}C]-and [$^{2}H_2$]-formaldehyde solution as shown in **Scheme 48**.



Scheme 48

Due to the high cost associated with ^{13}C-formaldehyde solution, it was diluted in a ratio of 60:40 with unlabelled formaldehyde and reacted with the phosphonate **56**. The progress of both the reactions were monitored by TLC and were judged to be complete in 1 h. Purification of the isotopically labelled compounds were carried out by eluting over silica gel to give a colourless oil. Both the compounds were analysed by GC and were found to be free of impurities. It is expected that the product will have a distribution of both single and double [^{13}C]-labelled methyl α-(hydroxymethyl)acrylate, together with some unlabelled material as shown below.



single labelled double labelled unlabelled

The cost of [^{13}C]-formaldehyde limited the preparation of **41c** to a small scale and therefore, only 0.5 g was prepared. The ^{1}H-NMR spectrum of **41c** is shown in **Figure 8**. The peak at 3.75 ppm is assigned to the methoxy group. The peak at 4.30 ppm, $^{3}J_{H\text{-}C}$ = 6.0 Hz, is due to the unlabelled $\mathbf{CH_2OH}$ group. The two peaks on either side of the central peak of 4.30 ppm are a doublet, $^{1}J_{H\text{-}C}$ = 159.9 Hz, associated with the labelled

$^{13}C\mathbf{H}_2OH$ group. Each of these peaks are further split by a long range $^3J_{H\text{-}C}$ coupling of 6.2 Hz. The signals associated with the protons of the C=C$\mathbf{H}_2$ vinyl group are observed at 5.83 and 6.23 ppm and each show a $^3J_{H\text{-}C}$ coupling of 4.2 Hz. The two doublets on either side of the peaks at 5.58 and 6.23 ppm are due to the protons of the labelled C=$^{13}C\mathbf{H}_2$ vinyl group and show large $^1J_{H\text{-}C}$ coupling of 107.0 and 117.0 Hz respectively

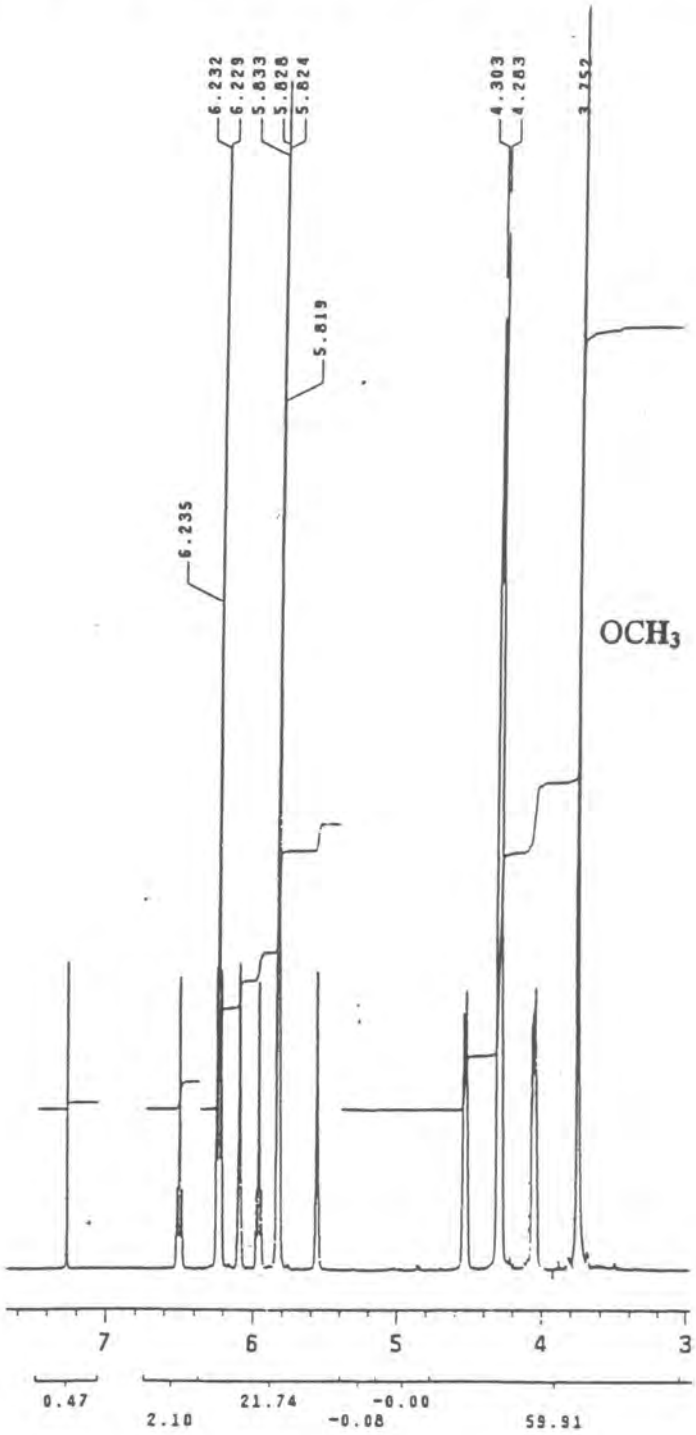


Figure 8 ^{1}H-NMR spectrum (299.9 MHz) of **41c**

The GC trace and the mass spectrum of **41c** are shown in **Figure 9.** It is clearly evident from the GC analysis that the sample is free of impurities. The mass spectrum shows the product contains a mixture of both the single and double [^{13}C]-labelled methyl α-(hydroxymethyl)acrylate together with some unlabelled material. The $[M]^+$ molecular ion 116 is due to the unlabelled methyl α-(hydroxymethyl)acrylate, whereas the $[M+1]^+$ molecular ion 117 arises as a result of single labelled compound. The $[M+2]^+$ molecular ion 118 is due to the double labelled methyl α-(hydroxymethyl)acrylate.

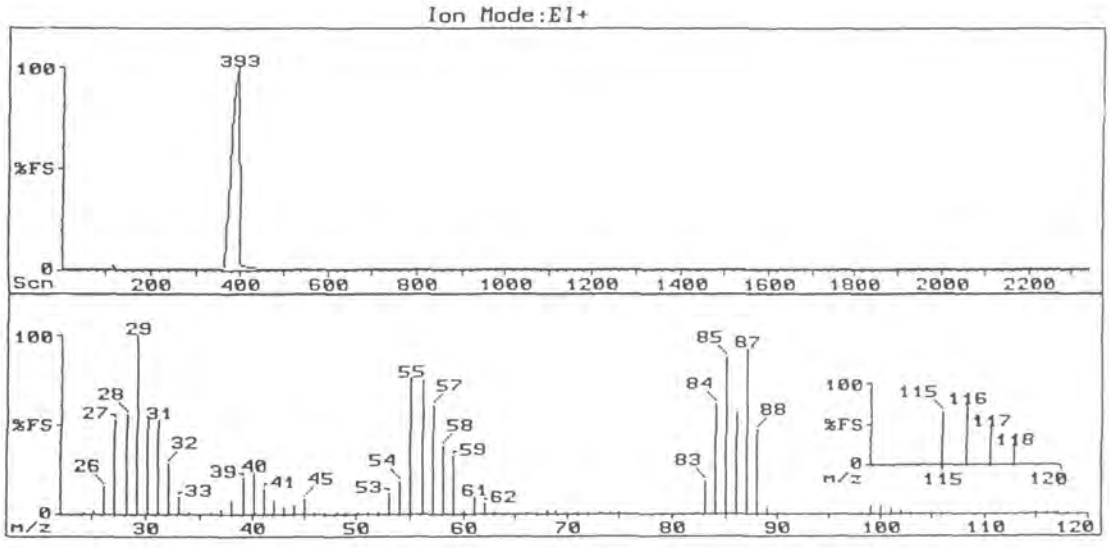


Figure 9 GC-MS of **41c**.

The preparation of the deuterated methyl hydroxymethylacrylate **41d** was, however, carried out on a larger scale (2 g) as [$^2H_2$]-formaldehyde is a relatively cheap compound. The ^{2}H-NMR spectrum of this material is shown in **Figure 10**. The peak at 4.30 ppm is attributed to CD_2OH group. The peaks at 5.87 and 6.28 ppm are of equal intensity and are due to the resonance from the vinyl deuteriums of the $C{=}CD_2$ group.

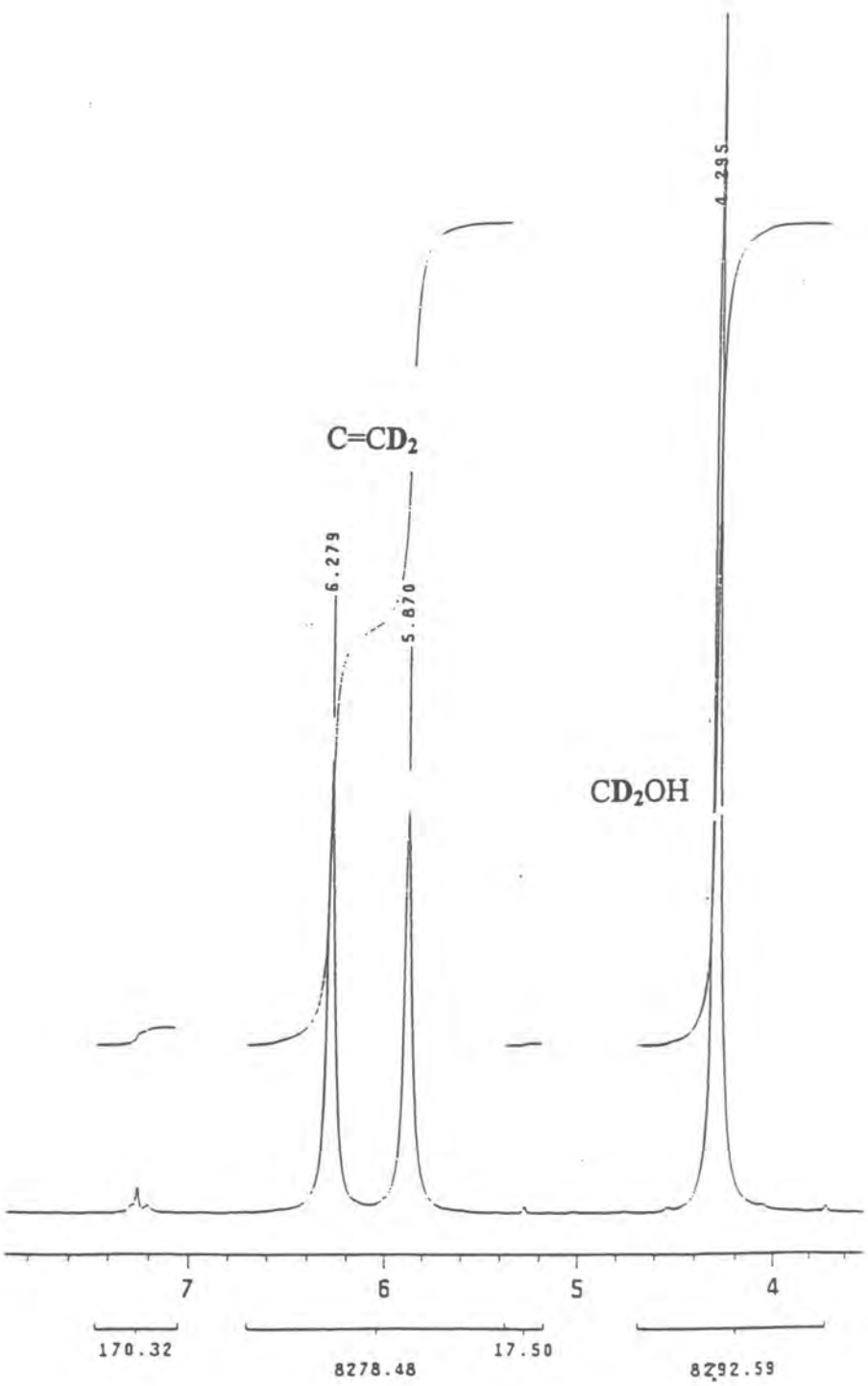


Figure 10 ^{2}H-NMR spectrum (46.0 MHz) of **41d**.

The mass spectrum of **41d** is shown in **Figure 11** and clearly shows the [M+4] molecular ion 120. The molecular ions 121 and 122 are possibly due to protonation of the [M+4] molecular ion.

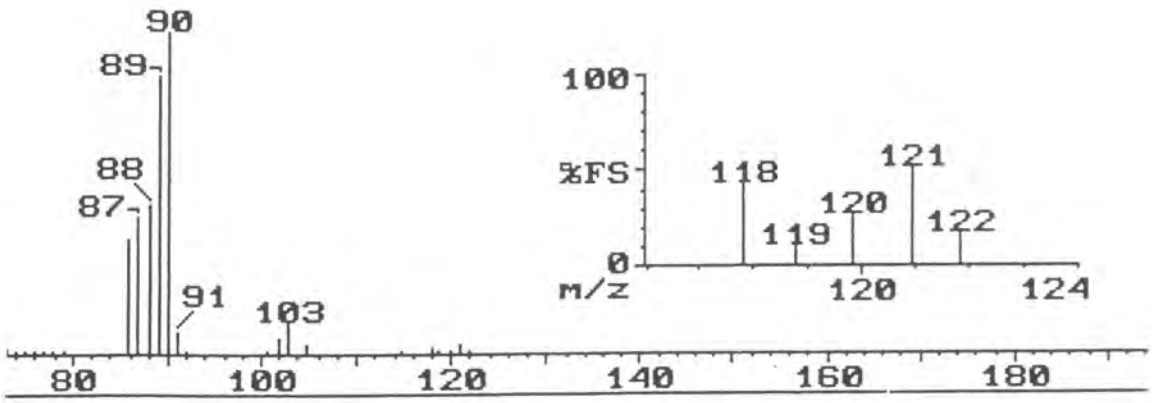


Figure 11 Mass spectrum of **41d**.

Having successfully prepared both the methyl [α-^{13}C]-(hydroxymethyl)-[3-^{13}C]-acrylate **41c** and methyl [α-$^{2}H_2$]-(hydroxymethyl)-[3-$^{2}H_2$]-acrylate **41d**, the next step was to generate copolymers with methyl methacrylate. The results of the copolymerisation studies are reported in Chapter 4

3.6 References

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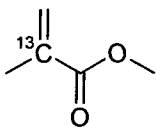
Chapter 4 Part 1

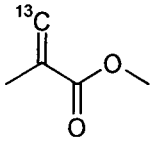
Polymerisation results of methyl [2-^{13}C]- and [3-^{13}C]-methacrylates

4.1 Introduction

In free radical polymerisation, termination by disproportionation introduces vinyl and saturated chain ends, whereas combination of two growing chains result in head to head links. The vinyl chain ends and the head to head links constitute weak links in PMMA.[1] In general, low intensity signals from these end groups and in particular ^{13}C-^{13}C coupling from the head to head links are difficult to detect without ^{13}C enrichment. However, introducing the ^{13}C isotope into MMA would clearly enhance these low intensity signals in the resultant polymer, therefore, making detection easier. In view of this, preparation of methyl [2-^{13}C]-methacrylate **1a** and methyl [3-^{13}C]-methacrylates **1b** respectively (99 atom %) became a key objective of this program to investigate the microstructure of the resultant polymers. The synthesis of these isotopically labelled monomers has been discussed in Chapter 2, Section 2.5.3 and 2.6.



1a



1b

4.2 Polymerisation results

Initially unlabelled MMA was polymerised to establish a working method for the polymerisation of methyl [2-^{13}C]- and [3-^{13}C]-methacrylate. The polymerisation was carried out in toluene solution for 4 hours at 80 °C using AIBN as the initiator. The viscous liquid obtained at the end of the polymerisation was dissolved in toluene and precipitated in hexane to give a white powder in modest yields. The procedure was repeated with both the methyl [2-^{13}C]- and [3-^{13}C]-methacrylate, **1a** and **1b**.

4.2.1 Molecular weights

The polymers prepared were analysed by GPC for molecular weights. It was noted that there were small differences in molecular weights between the isotopically labelled PMMA and the commercial material. However, these differences in molecular weights were not judged to be significant.

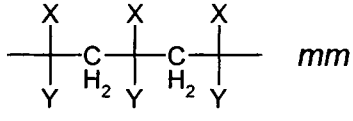
	Yield	Mw	Mn	Mw/Mn
Unlabelled PMMA	77 mg (28 %)	49000	24000	2.04
Poly(methyl [2-^{13}C] methacrylate	90 mg (34 %)	51000	29000	1.76
Poly(methyl [3-^{13}C] methacrylate	62.5 mg (23 %)	55000	31000	1.77

Table 11 Molecular weights and yields of PMMA prepared.

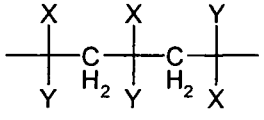
4.2.2 ^{13}C-NMR spectrum of unlabelled PMMA

The unlabelled PMMA was analysed by ^{13}C-NMR spectroscopy. For integration of the peaks in the spectrum to be reliable, all nuclei must relax to their equilibrium distribution between the successive pulses through interaction with the local fluctuating magnetic fields. Carbon bonded to hydrogen atoms relax slower than carbon atoms not so bonded and for this reason integration of the peaks are generally not performed. Additionally, due to the low abundance of ^{13}C nuclei (1.1 %), long accumulation times are needed to improve the signal to noise ratio.

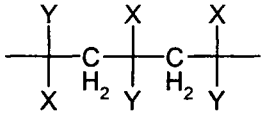
The general structure of poly(methyl methacrylate) can be simplified to, $[-CH_2CXY-]_n$ where X=Me and Y=CO_2Me. The ^{13}C-chemical shift of the α-methyl group and the quaternary carbon are influenced by the tacticity of a sequence of three monomer units (*triad*).



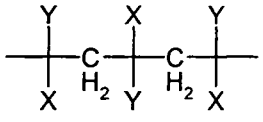
mm



mr



rm



rr

X= Me, Y=CO_2Me

As a consequence of tacticity, the ^{13}C-NMR spectrum of PMMA consists of three signals in the α-methyl region (16-21 ppm) due to triad splitting as shown in **Figure 12**.

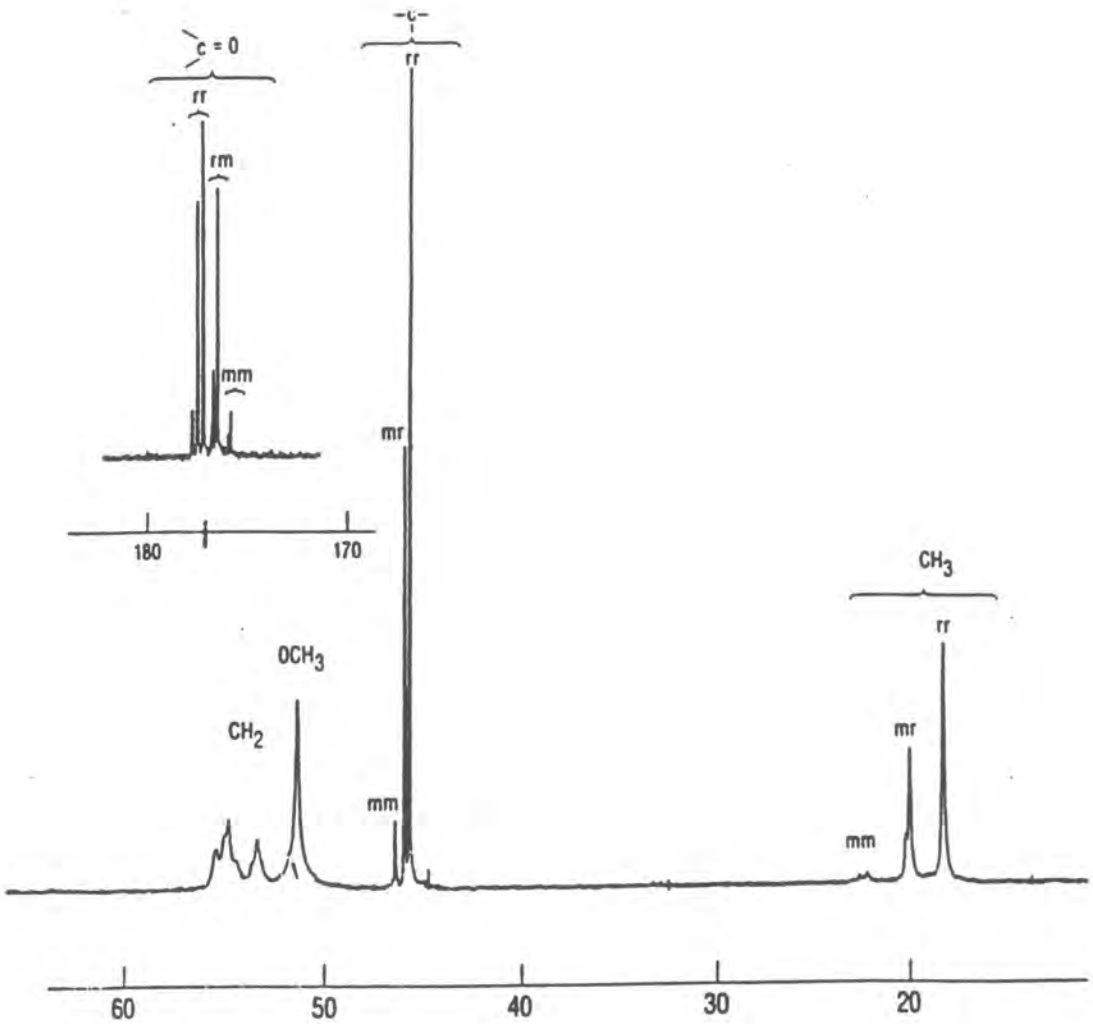


Figure 12 ^{13}C-NMR spectrum (125.6 MHz) of unlabelled PMMA.

Although there are four possible triad tacticity environments, *mm, mr, rm* and *rr*, only three peaks are observed in the ^{13}C-NMR spectrum as *mr* and *rm* are mirror images and therefore indistinguishable by NMR. Similarly the quaternary carbon is subjected to triad splitting resulting in three lines between 44-45 ppm.

The carbonyl group is influenced by tacticity of a sequence of five monomer units (*pentad*) as shown below.

mmmm	*(mmrm+mrmm)*	*rrrr*
(mmmr+rmmm)	*(mmrr+rrmm)*	*(mrrr+rrrm)*
rmmr	*(rmrm+mrmr)*	*rrrr*
	(rmrr+rrmr)	

The carbonyl region between 177.5-179.25 ppm consists of a number of peaks due to pentad splitting patterns, however, only six lines are resolvable by ^{13}C-NMR. The peak at 52.5 ppm is assigned to the methoxy group and this is observed as a singlet.

The chemical shift of the CH_2 group depends on the tacticity of its nearest neighbouring CXY groups. This would mean that there are two environments for the CH_2 group, namely *m* and *r* dyads resulting in two peaks in the ^{13}C-NMR spectrum of PMMA. The chemical shift of the CH_2 group is further influenced by the tacticity of a sequence of four monomer units (*tetrad*). There are a total of eight enantiomers of which six are distinguishable, namely, *mmm*, (*mmr*+*rmm*), *rmr*, *mrm*, (*mrr*+rrm) and *rrr*. As a result of dyad and tetrad splitting the signals for CH_2 groups are observed over the range 53-55 ppm.

4.2.3 ^{1}H-NMR spectrum of unlabelled PMMA

In the ^{1}H-NMR of unlabelled PMMA, **Figure 13**, three peaks are observed for the α-methyl group as a result of triad splitting. The peak with the greatest relative intensity at 0.8 ppm is assigned to the *rr* (syndiotactic) triad whereas the peak at 1.0 ppm is as a result of the (*mr*+*rm*) triad splitting. The peak of lowest intensity at 1.2 ppm is assigned to the *mm* (isotactic) triad. The peaks resulting from the resonance of the CH_2 groups are observed between 1.4 and 2.1 ppm. As the PMMA prepared in this study is by free radical initiation, it is expected that the polymer is predominantly syndiotactic in nature and therefore the two CH_2 environments are equivalent giving rise to a predominant peak at 1.8 ppm. The minor peaks at 1.4 ppm and 2.1 ppm indicate that there is some isotacticity in this PMMA. These peaks arise as a consequence of the non-equivalance

between the two protons of the CH_2 group. Finally, the singlet at 3.6 ppm is assigned to the methoxy group.

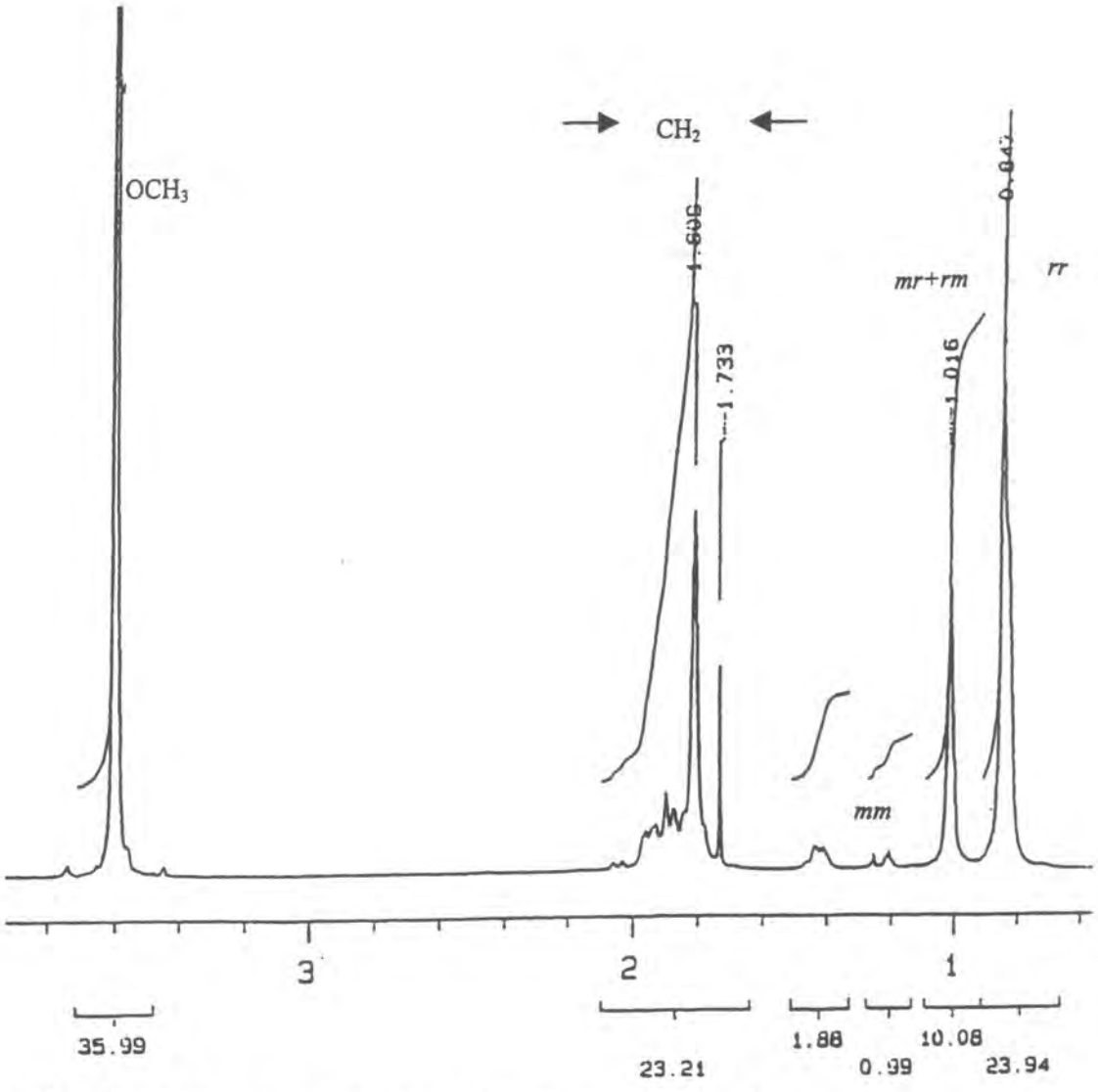


Figure 13 ^{1}H-NMR spectrum (499.9 MHz) of unlabelled PMMA.

4.2.4 ^{13}C and ^{1}H-NMR analysis of [^{13}C]-labelled PMMA

The ^{13}C-NMR of poly(methyl [2-^{13}C] methacrylate) is shown in **Figure 14** It is immediately apparent that signals from end groups are clearly observed due to isotopic enrichment. The peak at 137 ppm was assigned to the vinyl chain ends, whereas the signal at 34.5 ppm arises due to the saturated chain ends. Both of these end groups arise as a result of disproportionation reactions. Two additional peaks at 13 ppm and 34.5

ppm were observed which were absent from the ^{13}C-NMR spectrum of the unlabelled PMMA. These peaks are due to the presence of low levels of ethyl acrylate, copolymerising with the MMA. It was retrospectively deduced that this material was generated during the preparation of MMA from diethyl malonate and subsequently copolymerised with MMA. The peak at 13 ppm was assigned to the ester methyl group of the ethyl acrylate whereas, the CH_2 of the ethyl ester was observed at 58.5 ppm. The quaternary carbons were observed at 44 ppm and due to the ^{13}C enrichment, this peak was of the greatest relative intensity. The remaining peaks were consistent with the ^{13}C-NMR spectrum of PMMA prepared using commercial MMA.

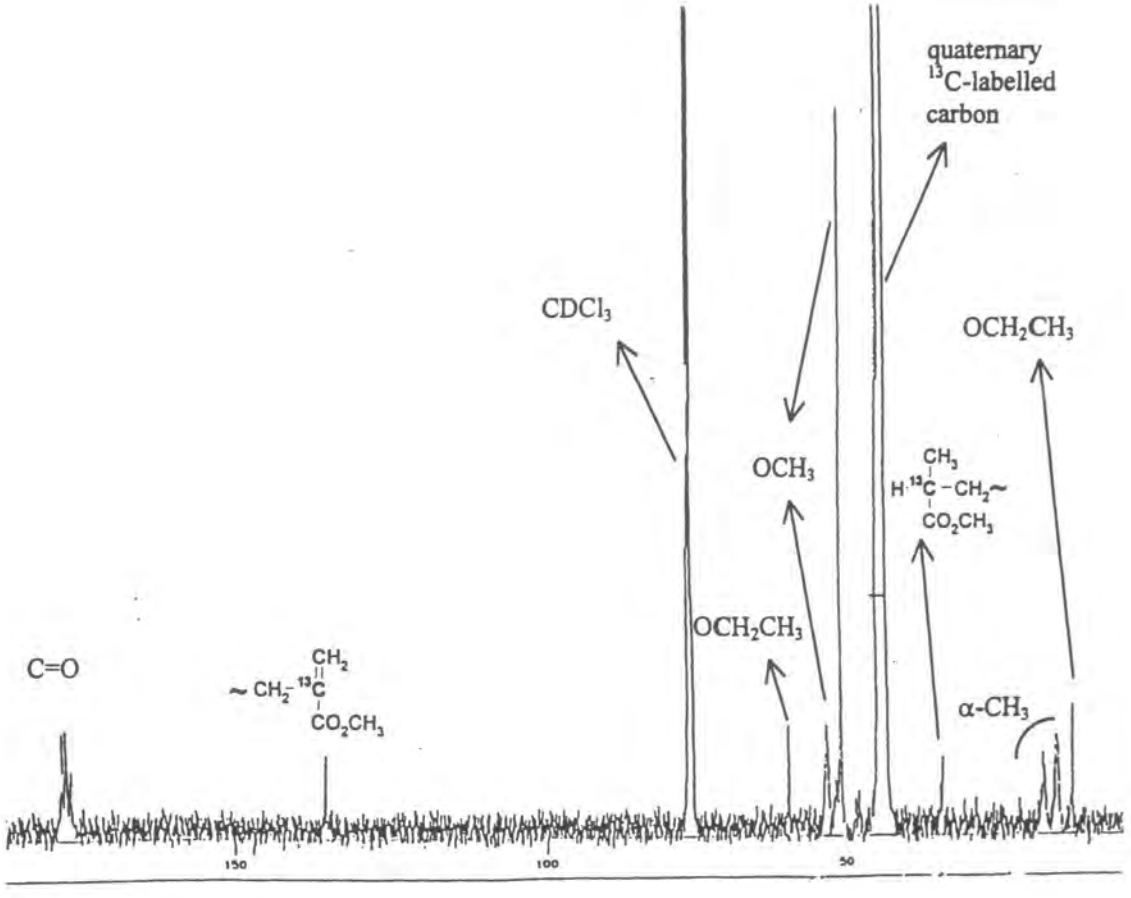


Figure 14 ^{13}C-NMR spectrum (100.5 MHz) of poly(methyl [2-^{13}C]-methacrylate).

In the ^{1}H-NMR spectrum of the poly(methyl [2-^{13}C]-methacrylate) shown in **Figure 15**, there was further evidence that ethyl acrylate had copolymerised with MMA. The methyl group of the ethyl ester is observed at 1.25 ppm and the CH_2 group at 4.05 ppm. Due to second order ^{1}H-^{13}C coupling the α-methyl and the backbone CH_2 regions are considerably broader when compared with the ^{1}H-NMR spectrum of unlabelled PMMA.

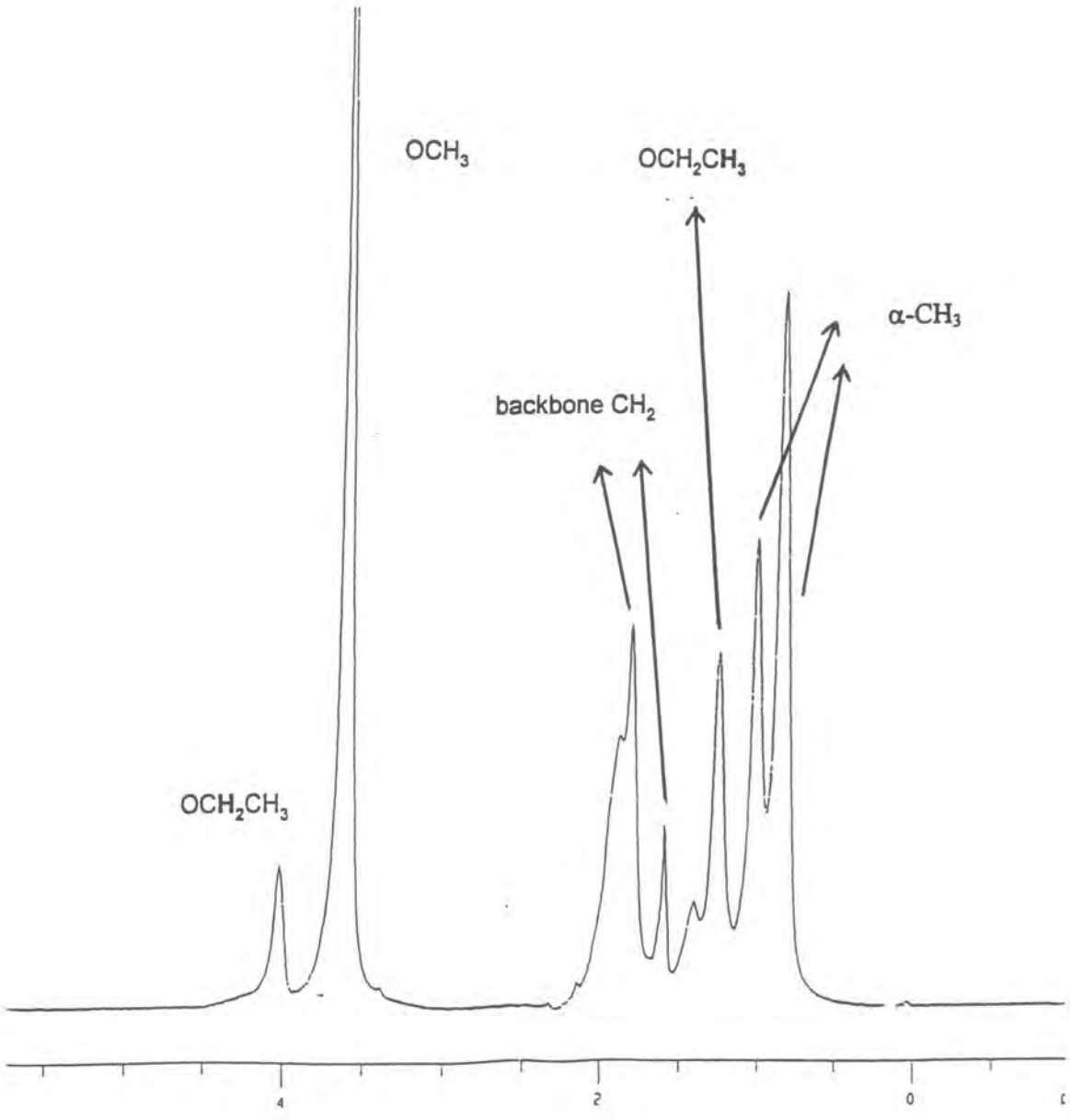


Figure 15 ^{1}H-NMR spectrum (400.1 MHz)) of poly(methyl [2-^{13}C]-methacrylate)

One of the key objectives in preparing and studying the ^{13}C-NMR of methyl [2-^{13}C]-methacrylate polymer was to search for ^{13}C-^{13}C coupling arising from coupling between quaternary carbons. However, there was no evidence of $^{1}J_{C\text{-}C}$ coupling in the spectrum of this polymer and therefore an attempt was made to study the polymer by a modified DEPT NMR technique in which only the quaternary carbons are brought into resonance (quaternary select ^{13}C-NMR), see **Figure 16**. An interesting feature of this spectrum is that four signals were observed between 49 ppm and 52 ppm suggesting the presence of labelled quaternary carbons within the polymer.

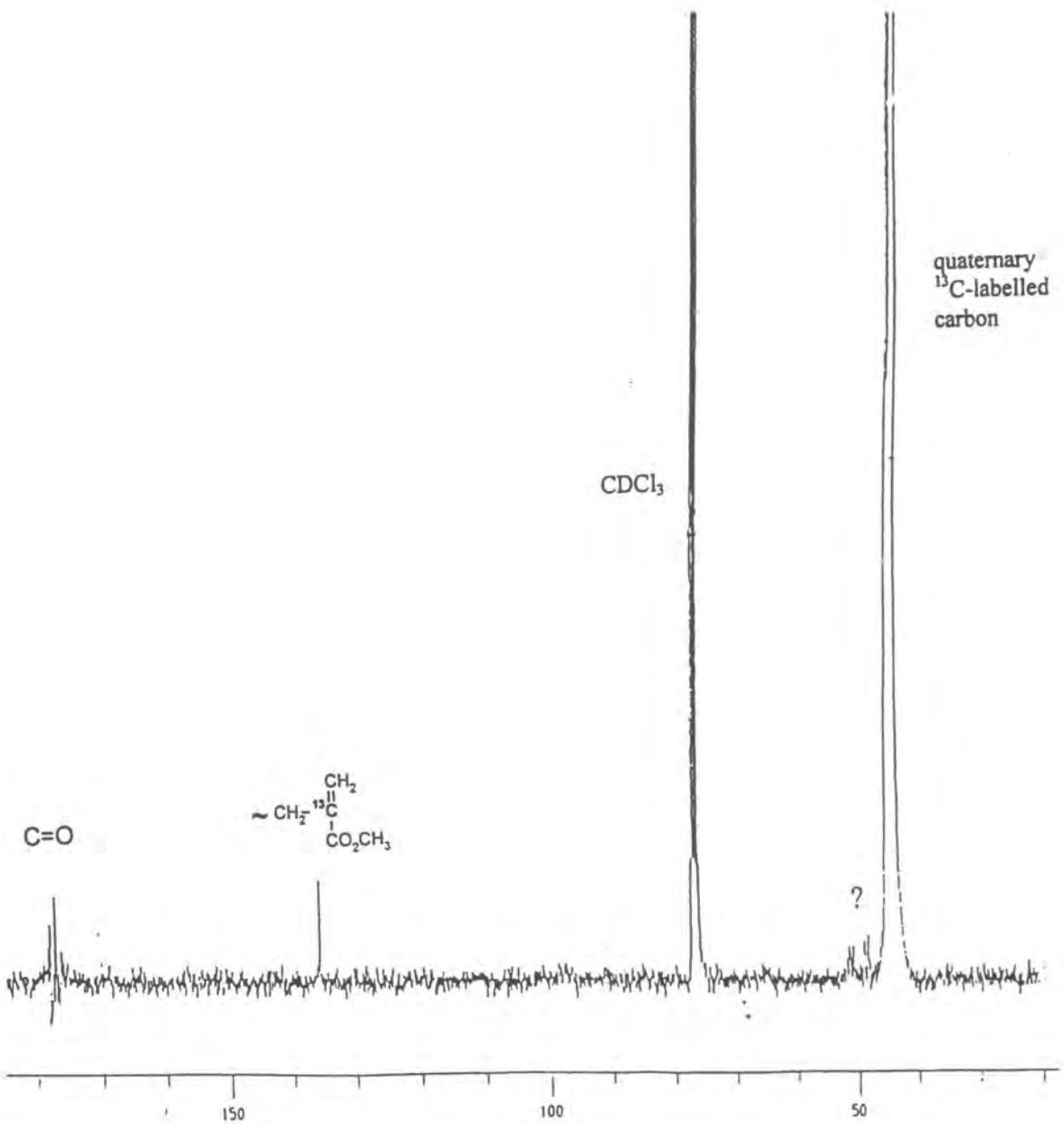


Figure 16 Quaternary select ^{13}C-NMR spectrum (75.5 MHz) of poly(methyl [2-^{13}C]-methacrylate).

In order to determine if these signals were associated with head to head links, the poly(methyl [2-^{13}C]-methacrylate) sample was heated to 200 °C in a DSC under nitrogen and held at this temperature for 20 minutes. Heating at this temperature is expected to decompose the head-head links.[2] The sample was then analysed to see the effect of heating on the four carbon-13 signals. **Figure 17** shows the resultant quaternary select ^{13}C-NMR spectrum of the polymer sample before and after heating.

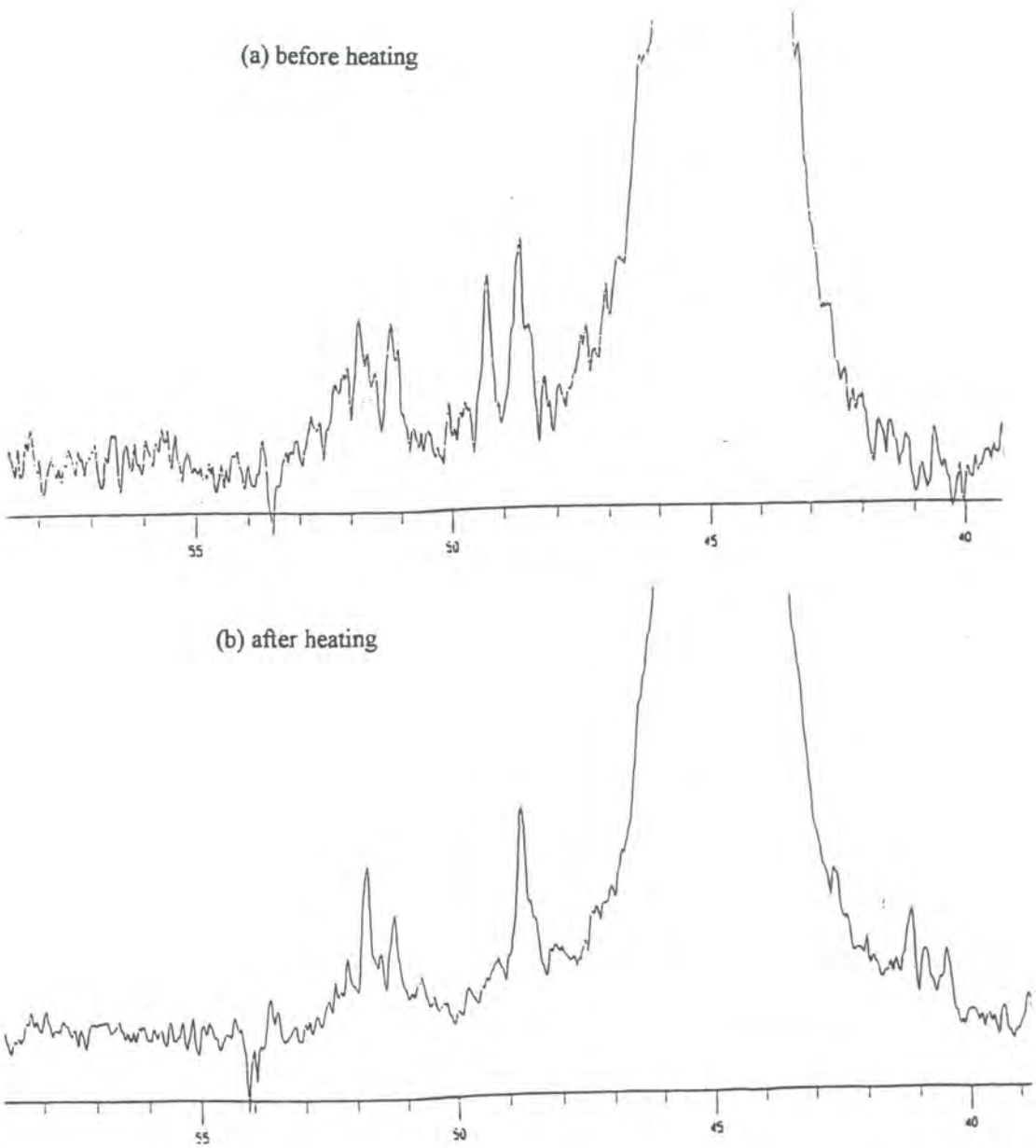


Figure 17 Resultant quaternary select ^{13}C-NMR spectrum (75.5 MHz) of the polymer sample derived from poly(methyl [2-^{13}C]-methacrylate) before (a) and after (b) heating to 200°C for 20 minutes under N_2.

On heating, it is clear from a comparison of the quaternary select ^{13}C-NMR spectrum, **Figure 17** (a) and (b) of the polymer sample derived from poly(methyl [2-^{13}C]-methacrylate) that the two peaks originally present between 48.8 and 49.5 ppm before heating, now appears as a singlet at 48.75 ppm. This may be as a consequence of the head to head link decomposing, resulting in the formation of a new environment in which the ^{13}C-labelled quaternary carbons are all now equivalent. However, the two peaks between 51 and 52 ppm remain relatively unaffected on heating.

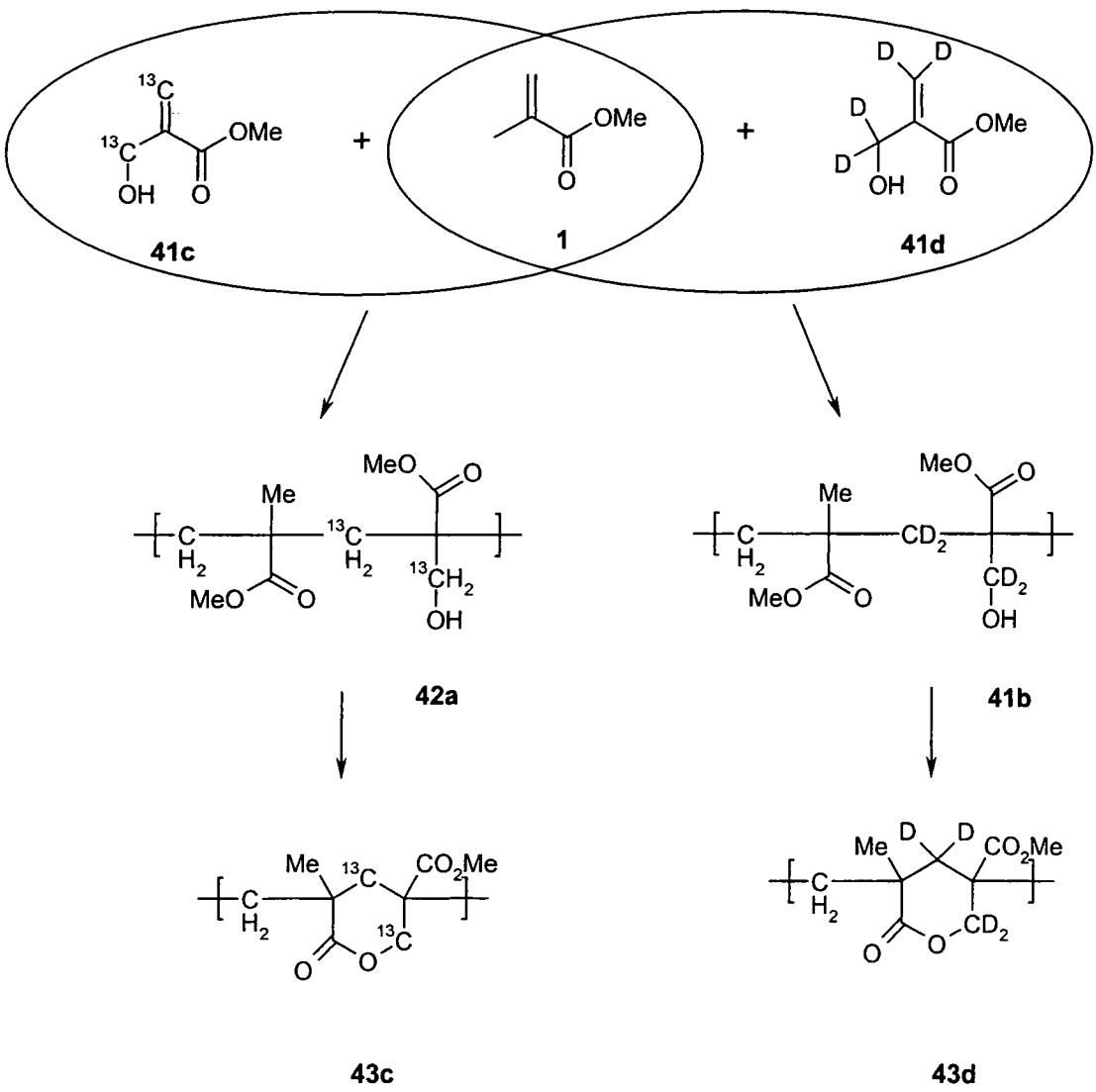
The ^{13}C-NMR spectra of methyl [3-^{13}C]-methacrylate **1b** polymer showed that the sample contained several impurities. In an attempt to purify this material, it was mixed with unlabelled PMMA at 10 wt. %. The polymer was then dissolved in toluene and precipitated from hexane. It was clear from ^{13}C and ^{1}H-NMR spectra that the material was significantly purer. Due to ^{13}C enrichment the CH_2 peak at 52.5-54.5 ppm was clearly enhanced. The saturated chain ends were still evident at 34.5 ppm, however, the vinyl chain ends were not observed. The ^{1}H-NMR was not significantly different to that of the unlabelled PMMA.

Chapter 4 Part 2

Copolymerisation studies of methyl methacrylate with isotopically labelled methyl α-(hydroxymethyl) acrylate

4.3 Introduction

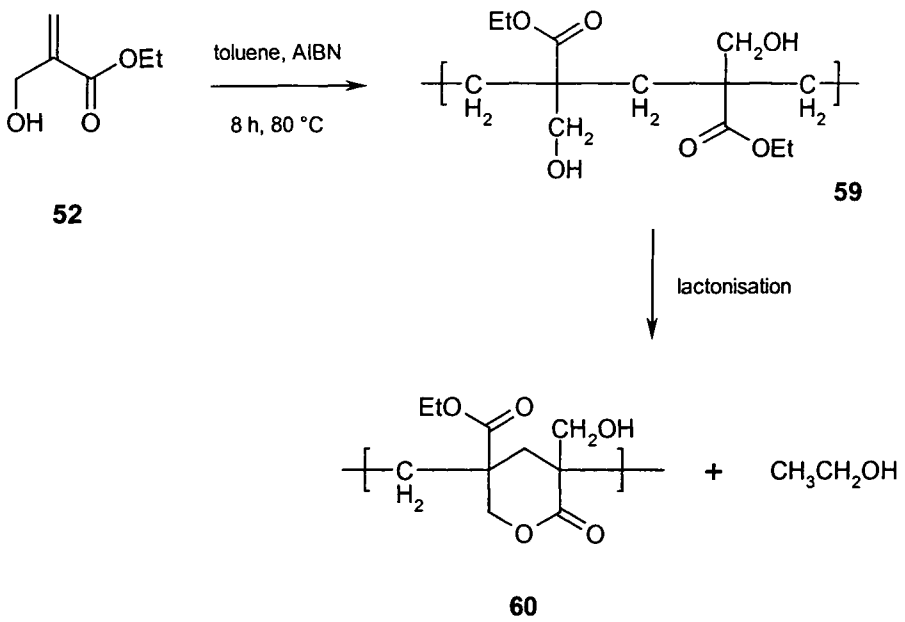
Copolymerisation of methyl α-(hydroxymethyl)acrylate (MHMA) **41** with methyl methacrylate **1** and subsequent acid treatment of the polymer introduces lactone rings along the polymer backbone. This material has desirable physical properties such as high *Tg* and good toughness. In order to study the extent of lactonisation in the copolymers of MMA, the preparation of methyl [α-^{13}C]-(hydroxymethyl)-[3-^{13}C]-acrylate, [$^{13}C_2$]-MHMA **41c** and methyl α-[$^{2}H_2$]-(hydroxymethyl)-[3-$^{2}H_2$]-acrylate, [$^{2}H_4$]-MHMA **41d** were carried out as shown in **Scheme 49**.



Scheme 49

4.4 Polymerisation of ethyl α-(hydroxymethyl)acrylate (EHMA)

Initial polymerisations were conducted with ethyl α-(hydroxymethyl)acrylate (EHMA) **52** due to difficulty in obtaining a sample of the required methyl α-(hydroxymethyl)acrylate (MHMA), see **Scheme 50**.



Scheme 50

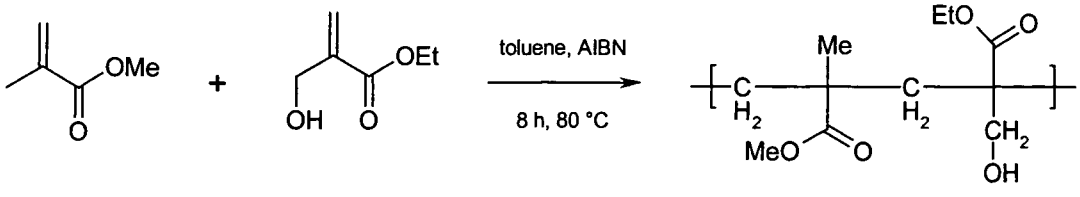
EHMA was polymerised in toluene solution at 80 °C for 8 hours. During the course of the polymerisation the polymer became insoluble and precipitated out. The polymer obtained was a gelatinous material and was dissolved in chloroform and precipitated from hexane. The polymer had a molecular weight of Mw 25000 and Mn 13500 as judged by GPC analysis.

An initial attempt to prepare the lactonised copolymer **60** using *p*-toluene sulphonic acid failed, however, the reaction was successful in a solvent mixture of toluene/methanol (3:1). The polymer **59** was initially soluble in the solvent system but on addition of a few drops of concentrated hydrochloric acid the polymer precipitated out. A small quantity of DCM was added to dissolve the precipitate, however, the system remained slightly cloudy. The reaction mixture was heated to 80 °C for 45 minutes and was then precipitated into hexane. The polymer was washed with de-ionised water and was dried

at 80 °C. The formation of lactone **60** was detected by ^{13}C-NMR from the downfield shift upon lactonisation of the CH_2OH group from 60 to 72 ppm.

4.5 Copolymerisation of methyl methacrylate with ethyl α-(hydroxymethyl)acrylate

A copolymer of MMA (0.75 g) with ethyl α-(hydroxymethyl)acrylate **52** (0.25 g) was prepared in dry toluene as shown in **Scheme 51**. The polymerisation was initiated using AIBN as the free radical initiator at 0.5 wt. % of the monomer. At the end of the reaction, the viscous liquid was precipitated into hexane.

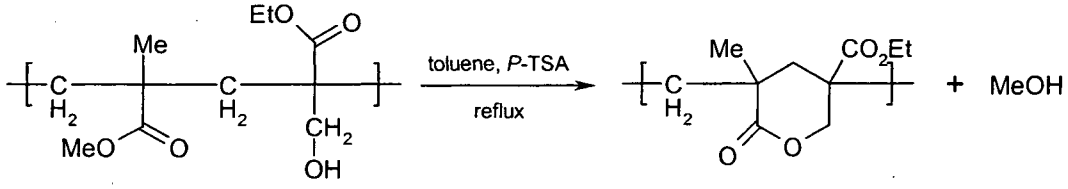


1 **52** **61**

Scheme 51

The copolymer **61**was then dried in an oven at 80 °C to constant weight (907 mg) and analysed by GPC. A copolymer of molecular weight Mw 63000 and Mn 37500 was obtained. The sharp peak at 1729 cm^{-1} in the FT-IR spectrum was assigned to be that of the carbonyl group and the broad peak at 3500 cm^{-1} was assigned to the hydroxyl group present in the copolymer. The peaks at 1245 cm^{-1} and 1037 cm^{-1} were of medium intensity and corresponded to the stretching C-O absorptions. In the resultant ^{13}C-NMR spectrum, the CH_2OH group was present as a broad peak at 60 ppm.

An attempted lactonisation using toluene/methanol (3:1) by adding a few drops of conc. hydrochloric acid failed. Therefore, *p*-toluene sulphonic acid was used as an alternative catalyst as shown in **Scheme 52**.



61 62

Scheme 52

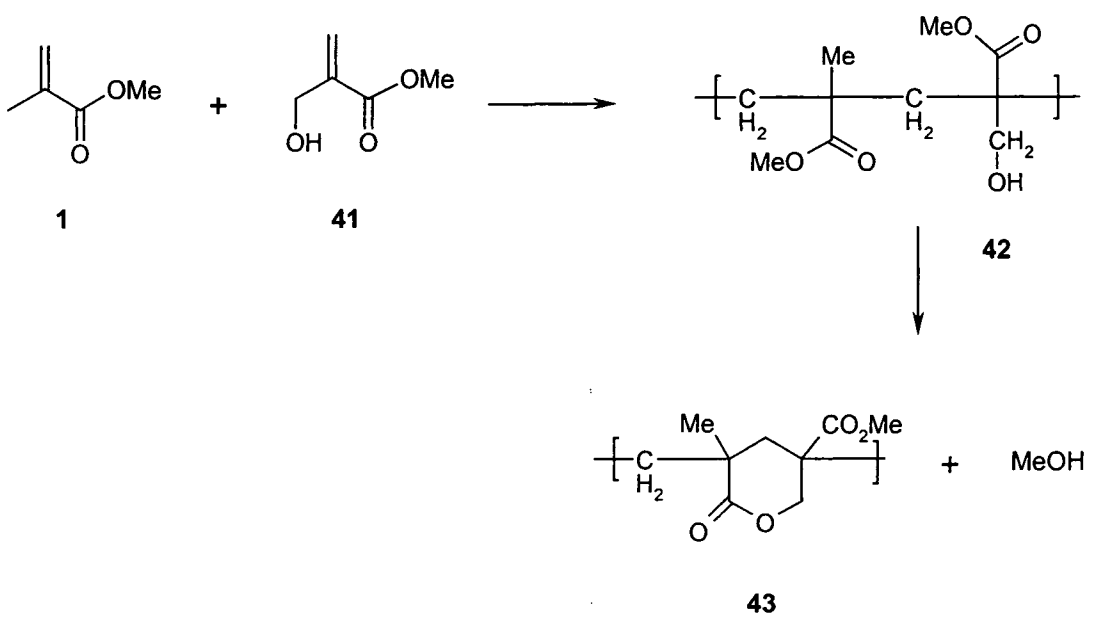
On heating to reflux the copolymer initially formed a solution and later precipitated out slowly during the course of the reaction. At the end of the reaction, the toluene was removed under reduced pressure and the polymer was dissolved in chloroform and precipitated into hexane. This procedure was repeated and the resultant copolymer was washed with de-ionised water to remove any acid residues and then dried at 80 °C to give a white powder. The dried copolymer became insoluble in chloroform and therefore d_6-DMSO was used to prepare a sample for ^{13}C-NMR analysis. It was clear from the spectrum that the peak at 60 ppm, originally attributed to that of the CH_2OH group, had disappeared, however, there was no evidence of the characteristic lactone peak at 72 ppm indicating that these groups have cross-linked to a large extent rather than lactonised in an intermolecular manner.

A final attempt at lactonising the copolymer was carried out by heating the copolymer in toluene/DCM (3:1) mixture at 80 °C for 45 minutes using a catalytic amount of conc. hydrochloric acid. From the ^{13}C-NMR analysis of the product it was clear that lactonisation had not taken place and therefore a copolymer with higher content of ethyl α-(hydroxymethyl)acrylate was prepared. The greater hydroxymethyl content was anticipated to increase the opportunity for the groups to cyclise. Accordingly, a reaction mixture consisting of 0.5 g MMA and 0.5 g EHMA was polymerised in toluene for 8 hours to give a material with a molecular weight of Mw 58000 and Mn 28000. Both ^{1}H and ^{13}C-NMR were consistent with that of the desired copolymer structure and attempts were then made to lactonise this material by heating to 80 °C for 1 hour in a toluene/methanol (2:1) solvent mixture using catalytic levels of concentrated hydrochloric acid. Analysis by ^{13}C-NMR of the resultant material once again indicated that lactonisation had failed. Despite some effort it was concluded that such copolymers are not amenable to lactonisation under our conditions.

4.6 Copolymerisation of methyl methacrylate with methyl α-(hydroxymethyl)acrylate (MHMA)

In the polymerisation reactions carried out so far, EHMA was used in place of MHMA. Due to difficulty encountered in achieving lactonisation of MMA/EHMA copolymer, it emerged important to substitute EHMA by MHMA. This would allow us to determine if the change from the ethyl to methyl ester is important and also develop a working method that could be applied to the copolymerisation of the isotopically labelled MHMA.

Our industrial sponsors were able to supply a sample of MHMA and with this in hand, efforts focused on generating copolymer **42** to assess its ability to lactonise, see **Scheme 53**.



Scheme 53

Attempts to generate a copolymer of MHMA with MMA in toluene failed and therefore the polymerisation was carried out in a more polar solvent mixture of toluene/methanol (3:1). It was once again clear from both ^{1}H and ^{13}C-NMR spectra that MHMA was reluctant to copolymerise and the sole product was primarily PMMA.

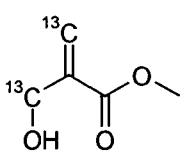
It is evident from the literature that copolymers of MHMA and styrene[3], EHMA and styrene[4], EHMA and MMA[5] have already been reported. Therefore, it was anticipated that it would be a straightforward process to prepare a copolymer of MHMA with MMA. A final attempt was therefore made under more forcing conditions in the absence of solvent.

The aim was to generate a copolymer of MMA and MHMA by reacting the monomers in a mole ratio of 60:40 respectively. In the absence of solvent the reaction proceeded efficiently, gelling in 25 minutes at 80 °C. Heating was continued for a further 1 h and 35 min and the product was isolated by dissolving in chloroform and precipitating from hexane. After further purification, the material was analysed by both ^{1}H and ^{13}C-NMR and was found this time to be consistent with the copolymer structure (discussed in detail later).

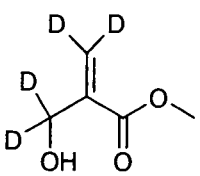
The lactonisation reaction was carried out in a toluene/methanol (1:1) solvent mixture. On addition of a few drops of conc. hydrochloric acid the solution turned cloudy and DCM was added to dissolve the precipitate. On heating to 80 °C over a duration of 45 minutes, the polymer slowly precipitated out as the lactonisation reaction took place. The resultant ^{1}H and ^{13}C-NMR spectra were found to be consistent with the lactonised copolymer structure (discussed in detail later).

4.7 Copolymerisation of methyl methacrylate with [$^{13}C_2$]- and [$^{2}H_4$]-methyl α-(hydroxymethyl)acrylate

Having established appropriate conditions to successfully prepare the lactonised MMA/MHMA copolymer, attention now focused on preparing samples using isotopically labelled, [$^{13}C_2$]-MHMA **41c** and [$^{2}H_4$]-MHMA **41d.**

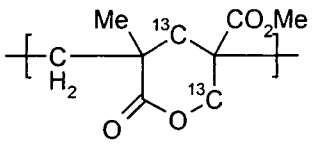


41c

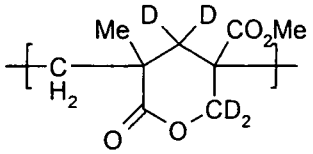


41d

The synthesis of **41c** and **41d** is described in Chapter 3, Section 3.5. The isotopically labelled MHMA's were then copolymerised separately with MMA and lactonised using the above established method to give **43c** and **43d**.



43c



43d

4.7.1 NMR results

It is useful to compare the differences in **Figure 18** and **19** as the deuterated sites which are associated with MHMA in **Figure 19** are absent from the spectrum in **Figure 18**. In both ^{1}H-NMR spectra, the α-methyl groups are observed in the region between 0-1.5 ppm. The signal due to the CH_2 groups in the polymer chain of the MMA/MHMA copolymer is observed between 1.5-2.5 ppm, see **Figure 18**. The polymer chain of the MMA/[$^2H_4$]-MHMA copolymer consists of a CD_2 group and does not appear in the ^{1}H-NMR spectrum. Therefore, the signal observed between 1.5-2.5 ppm is now assigned to the CH_2 group of MMA. The resonance from the methoxy group is observed between 3.2-3.8 ppm. The ^{1}H-NMR of the MMA/MHMA copolymer consisted of a shoulder between 3.9-4.1 ppm adjacent to the peak attributed the OCH_3 group. Importantly, this signal is absent in the ^{1}H-NMR of the MMA/[$^2H_4$]-MHMA copolymer, indicating that it is due to the CH_2OH groups. This labelling study allows us to securely assign the backbone CH_2 and CH_2OH groups.

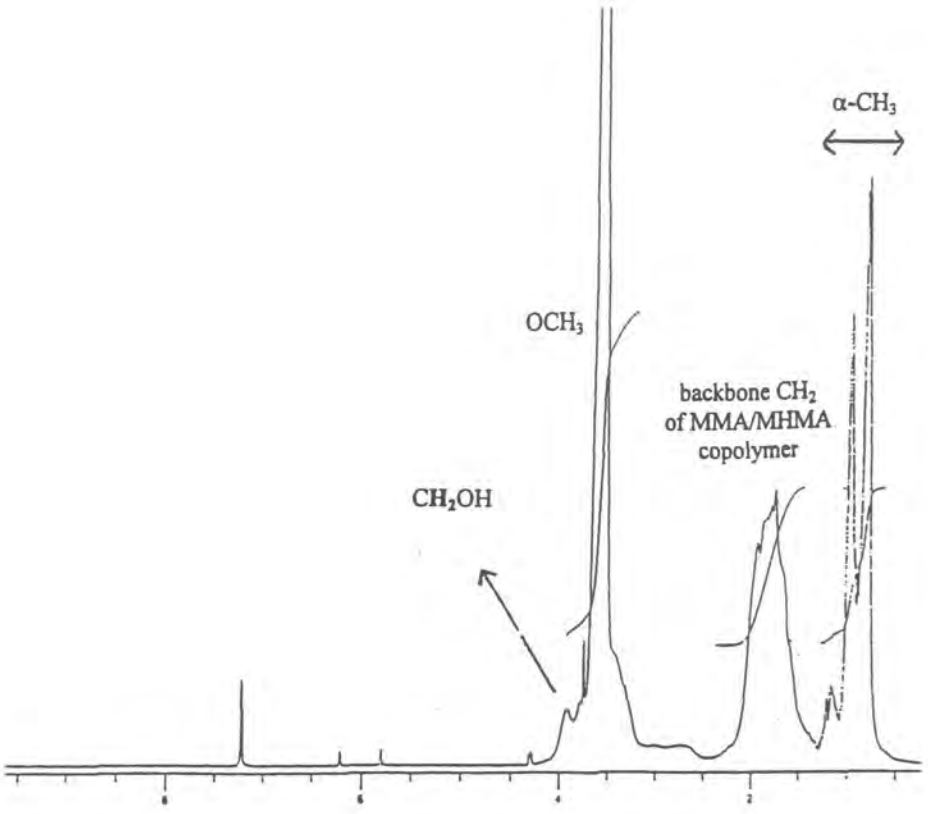


Figure 18 ^{1}H-NMR spectrum (300.4 MHz) of MMA/MHMA copolymer before lactonisation.

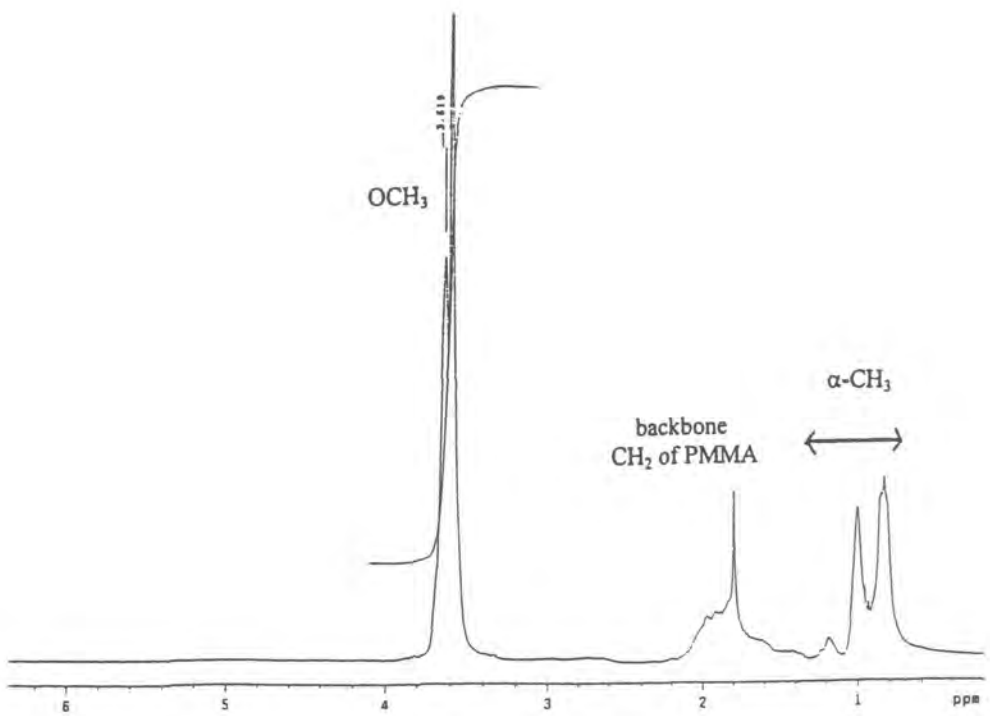


Figure 19 ^{1}H-NMR spectrum (299.9 MHz) of MMA/[$^{2}H_4$]-MHMA copolymer before lactonisation.

The ^{1}H-NMR spectra of MMA/MHMA and MMA/[$^2H_4$]-MHMA copolymers after lactonisation are shown in **Figures 20** and **21** respectively. The α-CH_3, backbone CH_2 and the OCH_3 groups are observed between 0-1.5 ppm, 1.5-2.5 and 3-3.9 ppm repetively. The ^{1}H-NMR spectrum shown in **Figure 20** of the lactonised MMA/MHMA copolymer indicates that the signal from this CH_2OH group shifts downfield after lactonisation due to the electron withdrawing effect of the carbonyl group. The peak resulting from the resonance of the CH_2O- group was 'bimodal' in appearance and was observed between 3.9-4.75 ppm. This peak was not observed in the ^{1}H-NMR spectrum of the MMA/[$^2H_4$]-MHMA copolymer due the presence of the deuterium isotope.

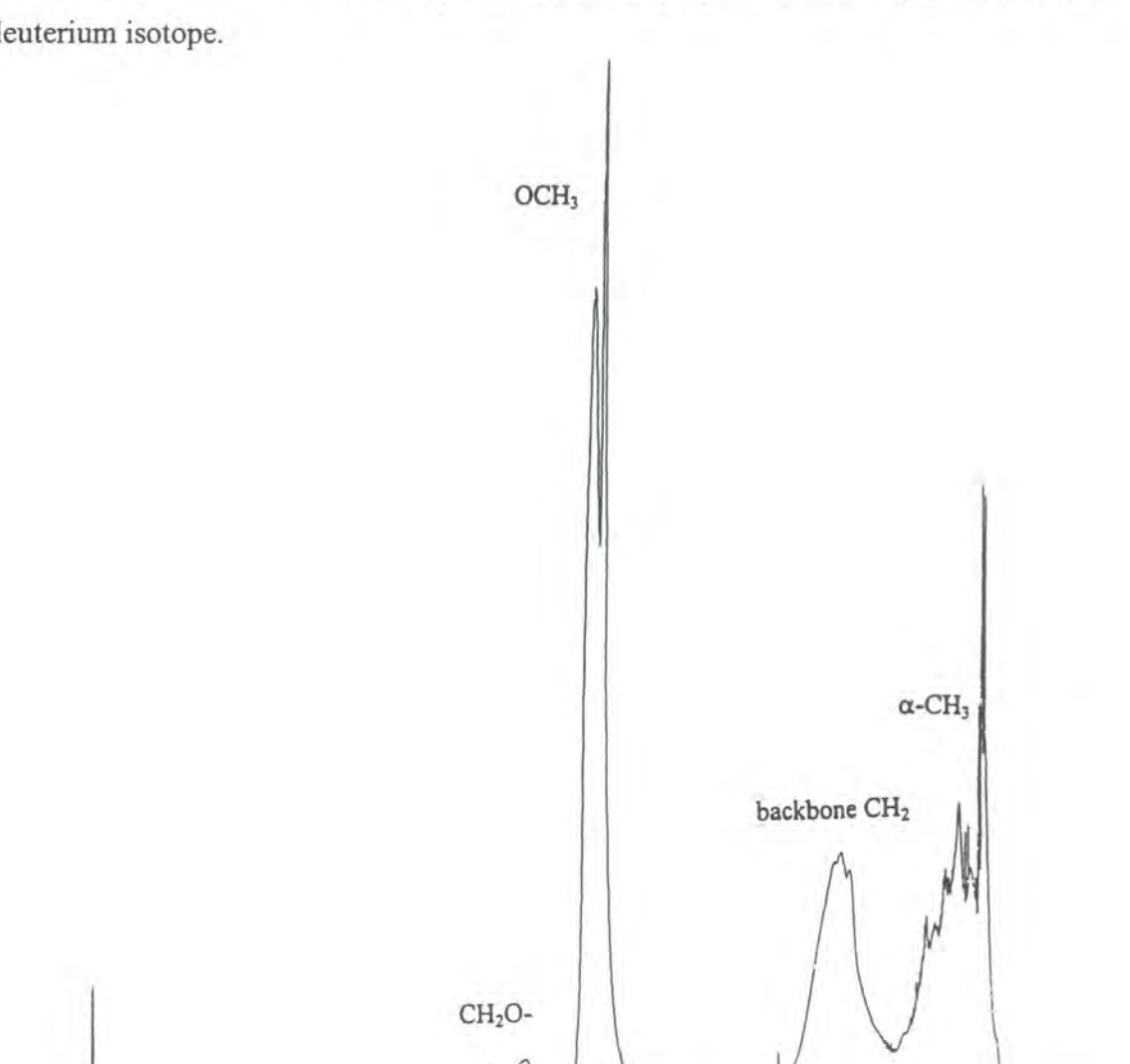


Figure 20 ^{1}H-NMR spectrum (300.4 MHz) of MMA/MHMA copolymer after lactonisation.

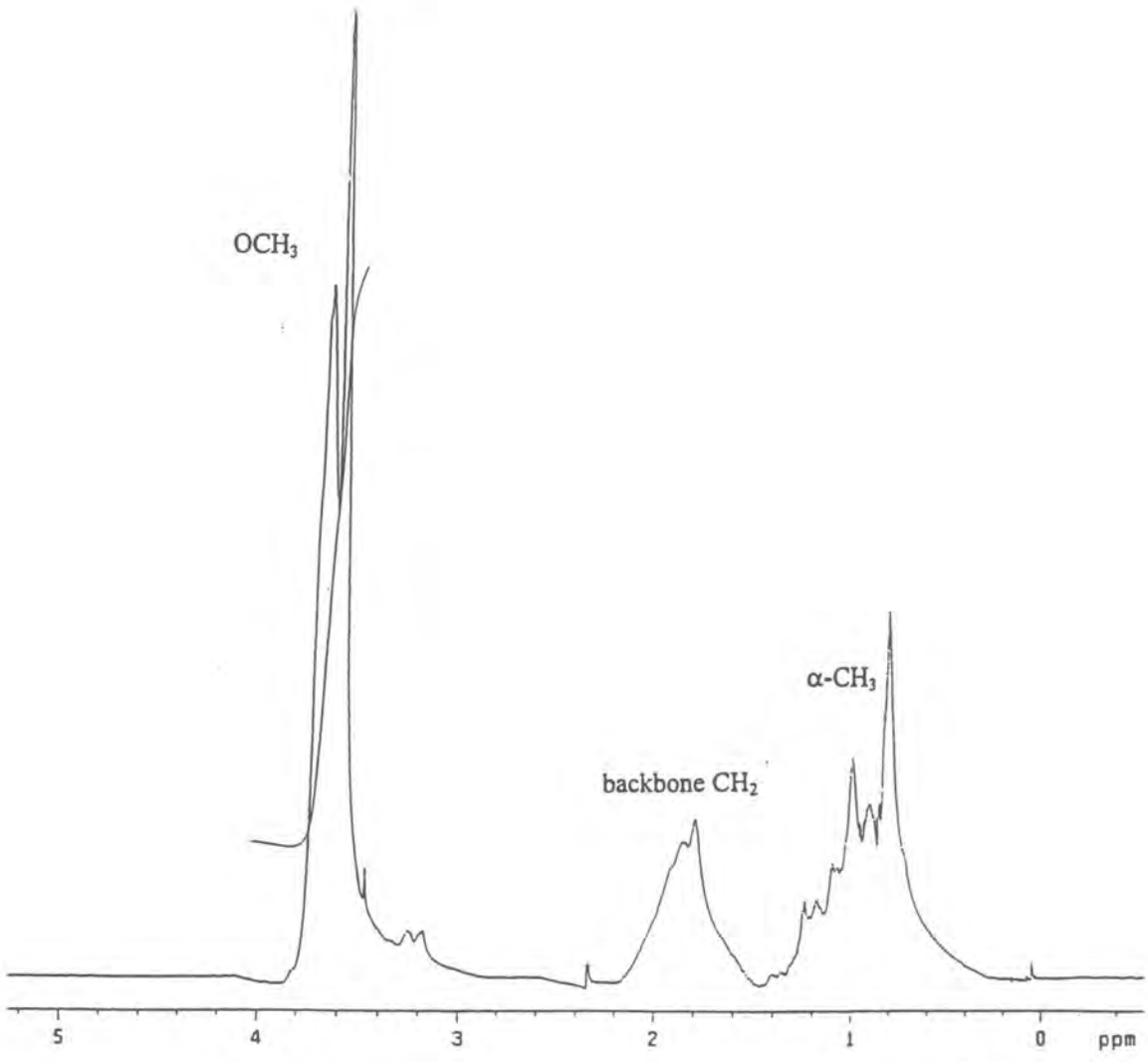


Figure 21 ^{1}H-NMR spectrum (299.9 MHz) of MMA//[$^{2}H_4$]-MHMA copolymer after lactonisation.

The ^{2}H-NMR spectra of MMA/[$^{2}H_4$]-MHMA copolymers before and after lactonisation were broad and bimodal in appearance, see **Figures 22** and **23**. The peak at 3.8 ppm in the ^{2}H-NMR spectrum of the copolymer before lactonisation, **Figure 22**, was assigned to the $\mathbf{CD_2OH}$ group and was found to shift downfield to 4.2 ppm after lactonisation, **Figure 23**. The backbone $\mathbf{CD_2}$ group was observed in both of the ^{2}H-NMR spectra before and after lactonisation in the region of 2 ppm as expected.

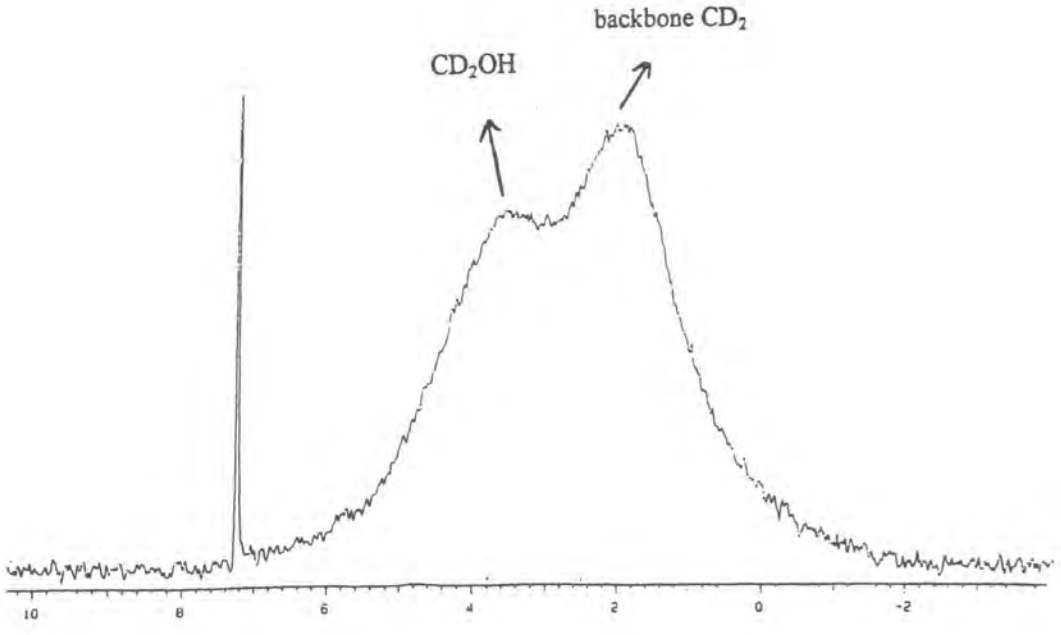


Figure 22 ^{2}H-NMR spectrum (76. 7 MHz) of MMA/[$^2H_4$]-MHMA copolymer before lactonisation.

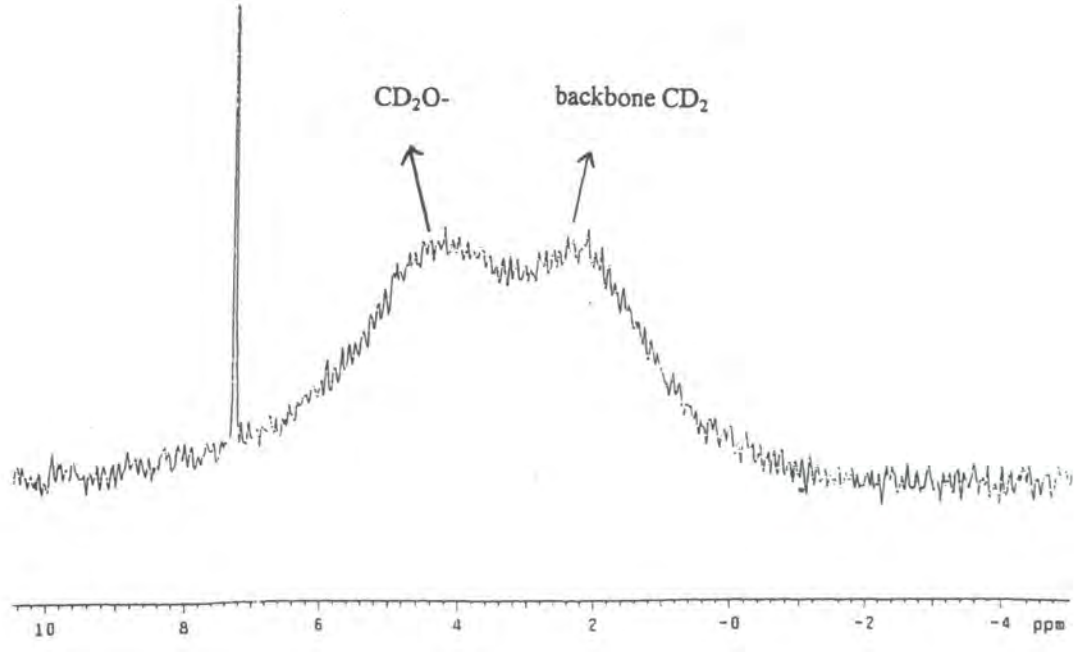


Figure 23 ^{2}H-NMR spectrum (76.7 MHz) of MMA/[$^2H_4$]-MHMA copolymer after lactonisation.

The ^{13}C-NMR spectrum of the MMA/MHMA copolymer before lactonisation is shown in **Figure 24**. The signals in the region between 16-22 ppm are assigned to the methyl groups, whereas those between 174-182 ppm were assigned to the carbonyl carbons. A ^{13}C-DEPT 135 NMR experiment was then carried out to identify the peaks present in the expanded region between 40-64 ppm.

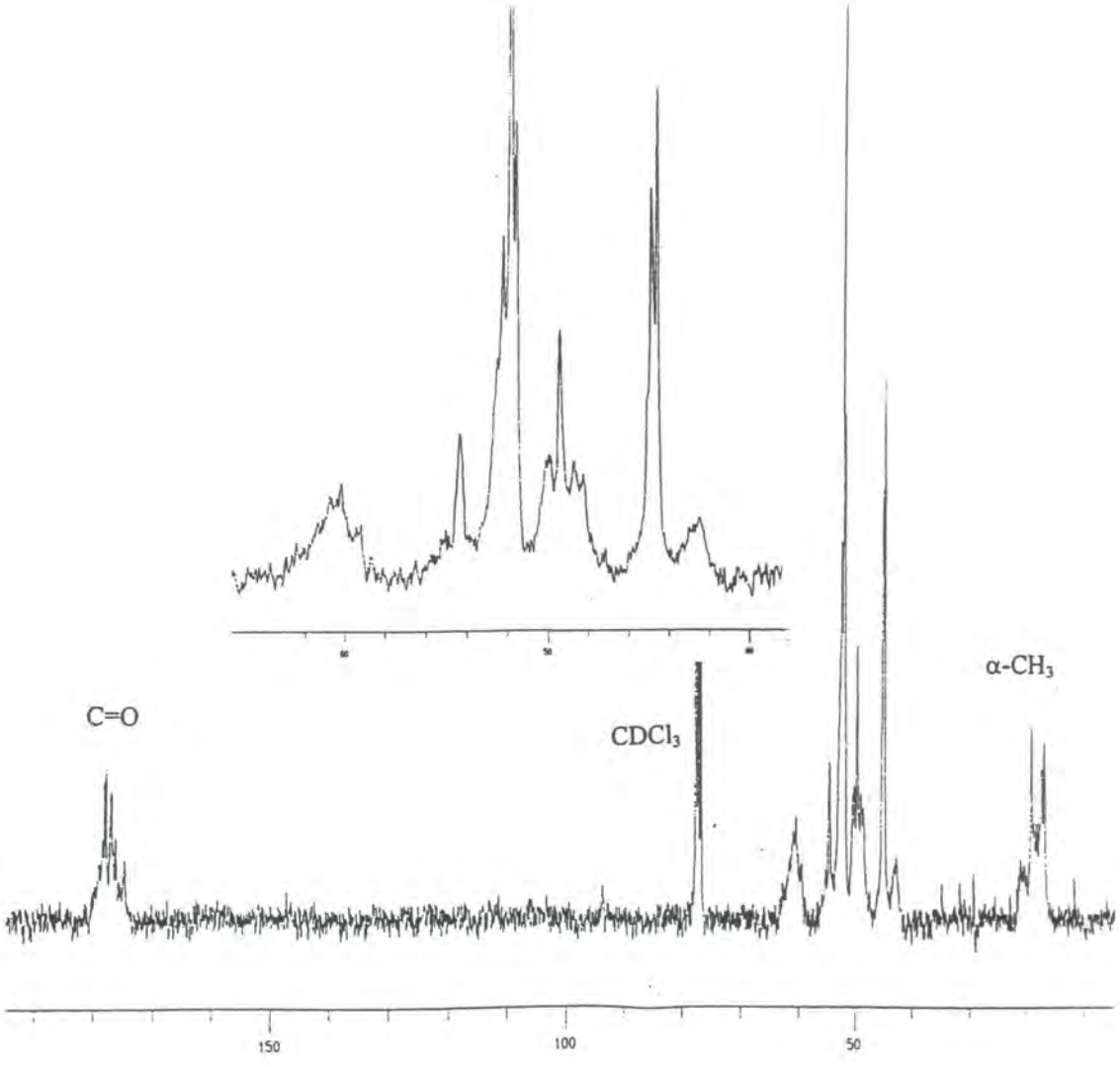


Figure 24 ^{13}C-NMR spectrum (75.6 MHz) of unlabelled MMA/MHMA copolymer before lactonisation.

The resultant ^{13}C-DEPT 135 NMR spectrum obtained is shown in **Figure 25**. It is immediately clear that the peak present originally at 45 ppm in **Figure 24** is absent indicating that this signal is due the quaternary carbon and that the peak observed at 52.5 ppm was due to the methoxy groups. The resonance from the CH_2OH groups were

observed between 58.5 and 63 ppm. The remaining three signals observed between 41-44 ppm, 47-50 ppm and 54-55 ppm were clearly due the CH_2 groups on the polymer backbone in three different environments. The copolymer of MMA and MHMA is therefore not random or alternating and appears to consist of small sequences of blocks of each monomer. The peak between 54-55 ppm was assigned to CH_2 groups from short sequences of MMA monomer units along the polymer chain. In order to securely assign the peaks between 41-44 ppm and 47-50 ppm seen in **Figure 25**, a ^{13}C DEPT 45 NMR spectrum of MMA/[$^{13}C_2$]-MHMA copolymer before lactonisation was recored

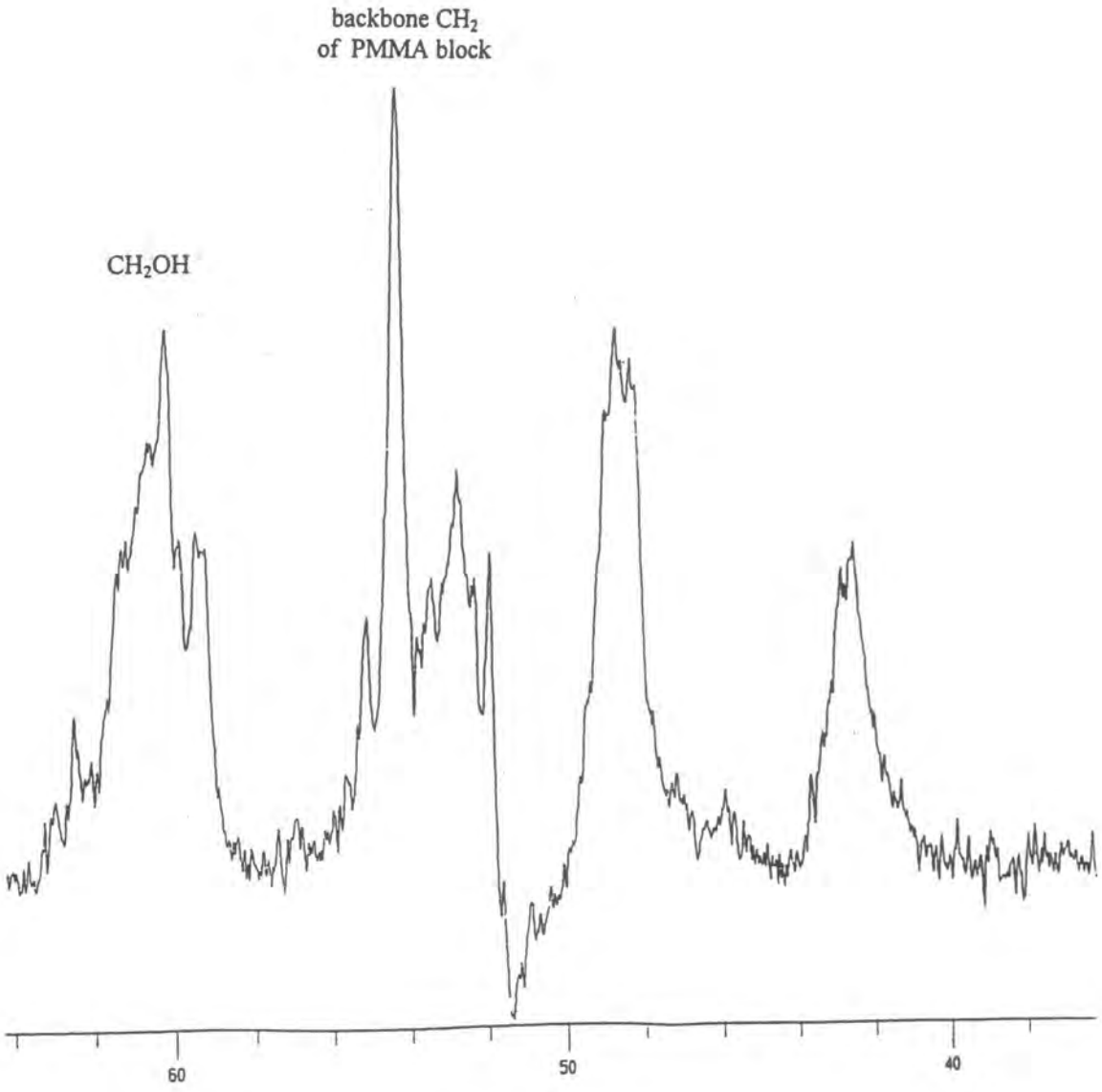


Figure 25 ^{13}C DEPT 135 NMR spectrum (75.5 MHz) of the unlabelled MMA/MHMA copolymer before lactonisation

Figure 26 shows the resultant ^{13}C DEPT 45 NMR spectrum of MMA/[$^{13}C_2$]-MHMA copolymer before lactonisation. An interesting feature of this spectrum is that the peaks between 54-55 ppm assigned originally to the CH_2 groups from short sequences of MMA monomer units along the polymer chain are weak because the resonance from the CH_2 moiety is due only to the natural abundance (^{13}C, 1.1 %). The signal from the labelled $^{13}CH_2$ groups from the short sequences of the [$^{13}C_2$]-MHMA monomer units were observed between 41-44 ppm whereas the signals from the CH_2 and labelled $^{13}CH_2$ groups between MMA and MHMA units were observed between 47-50 ppm.

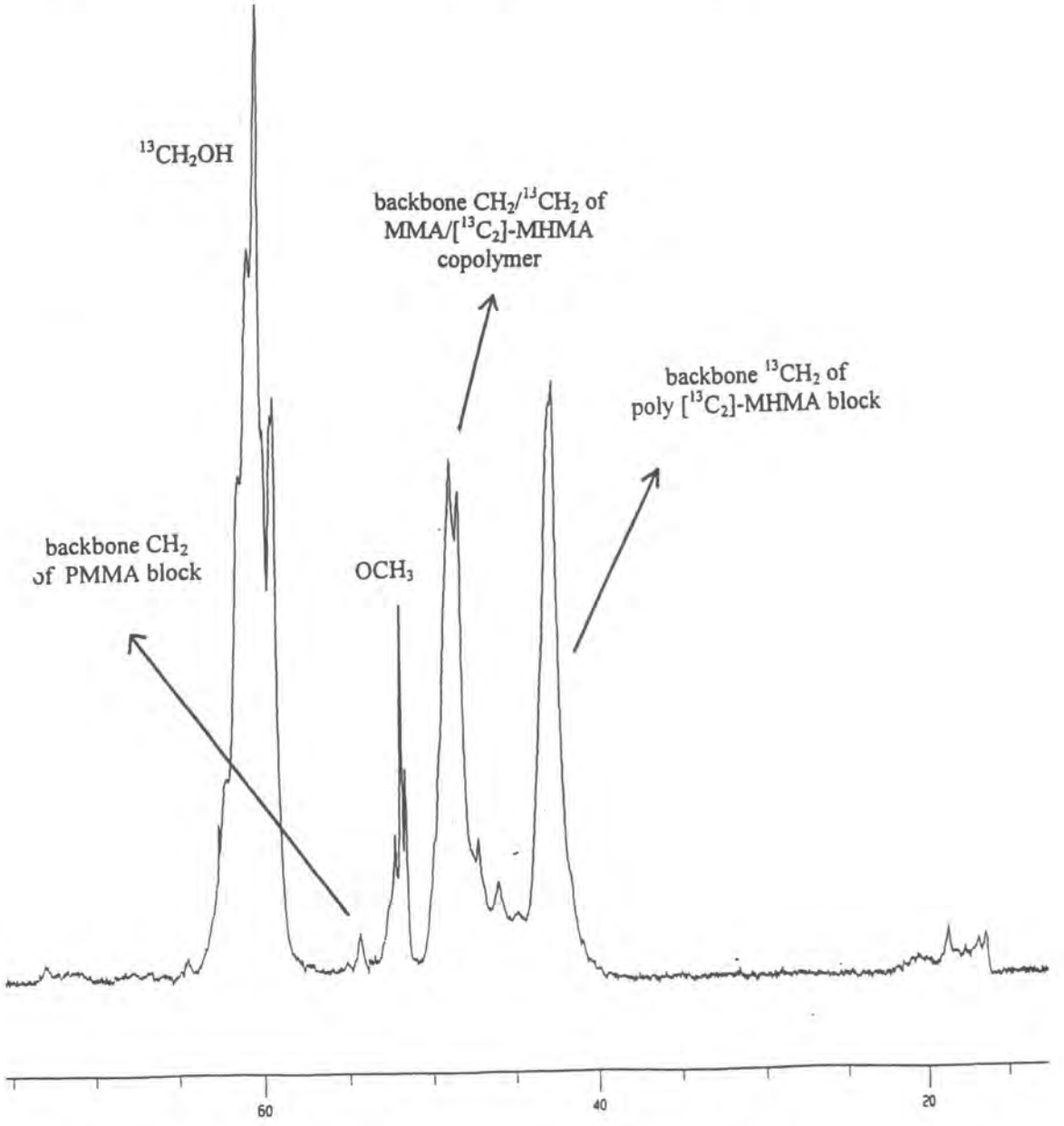


Figure 26 ^{13}C-NMR DEPT 45 spectrum (75.5 MHz) of the MMA/[$^{13}C_2$]-MHMA copolymer before lactonisation.

In order to assess the extent of lactonisation, a ^{13}C-NMR spectrum of lactonised MMA/[$^{13}C_2$]-MHMA copolymer was recorded, see **Figure 27**. The methyl groups attached to the MMA unit is observed between 16-19 ppm, a shift of about 3 ppm upfield compared with the unlactonised copolymer. There seems to be a similar effect upon lactonisation on the carbonyl groups which is shifting the signal upfield to between 172-178 ppm. In order to assign the remaining peaks, a ^{13}C DEPT 135 NMR of the MMA/[$^{13}C_2$]-MHMA copolymer after lactonisation was recorded

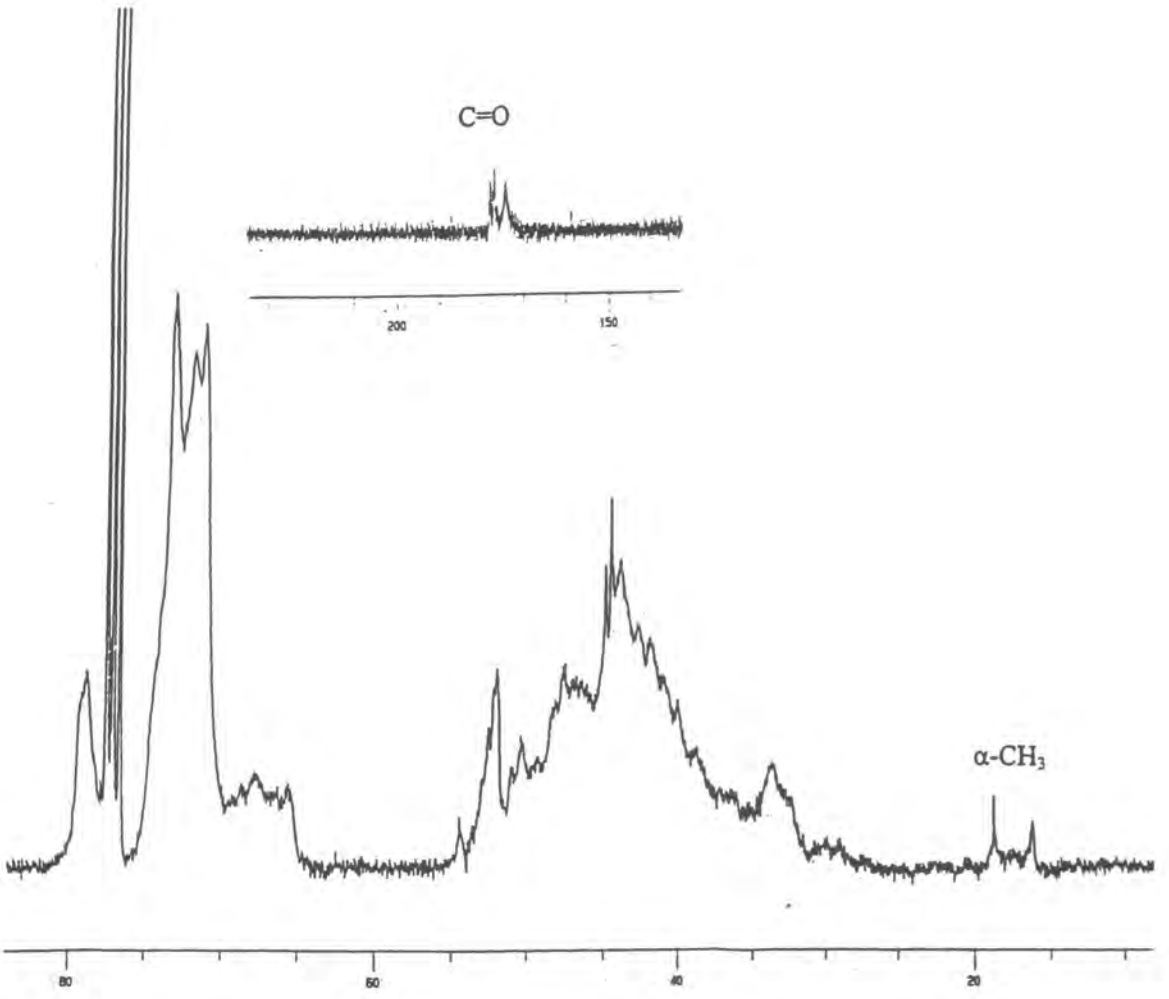


Figure 27 ^{13}C-NMR spectrum (75.5 MHz) of MMA/[$^{13}C_2$]-MHMA copolymer after lactonisation.

The resultant ^{13}C DEPT 135 NMR spectrum of the MMA/[$^{13}C_2$]-MHMA copolymer after lactonisation is shown in **Figure 28.** The peak around 52.5 ppm was assigned to the methoxy group and more interestingly the CH_2 groups from the short sequences of MMA units were still evident between 54-55 ppm. The $^{13}CH_2$ enriched groups of the [$^{13}C_2$]-MHMA units and CH_2 group of the MMA, together with the quaternary carbon were observed as a broad peak between 37.5-51 ppm. The $^{13}CH_2$ group from the small sequences of the MHMA units were present between 32-35 ppm. It is clear from the spectrum that complete lactonisation had taken place, as there is no signal due to the free CH_2OH groups. Upon lactonisation this group shifts upfield to between 70-76 ppm. However, there are two signals on both sides of this peak indicating that the CH_2O-groups are in two chemically different environments. The lactonisation of the short MHMA/MHMA blocks present in the copolymer may account for one the peaks while the other peak may perhaps arrive as a result of the CH_2OH group cross-linking.

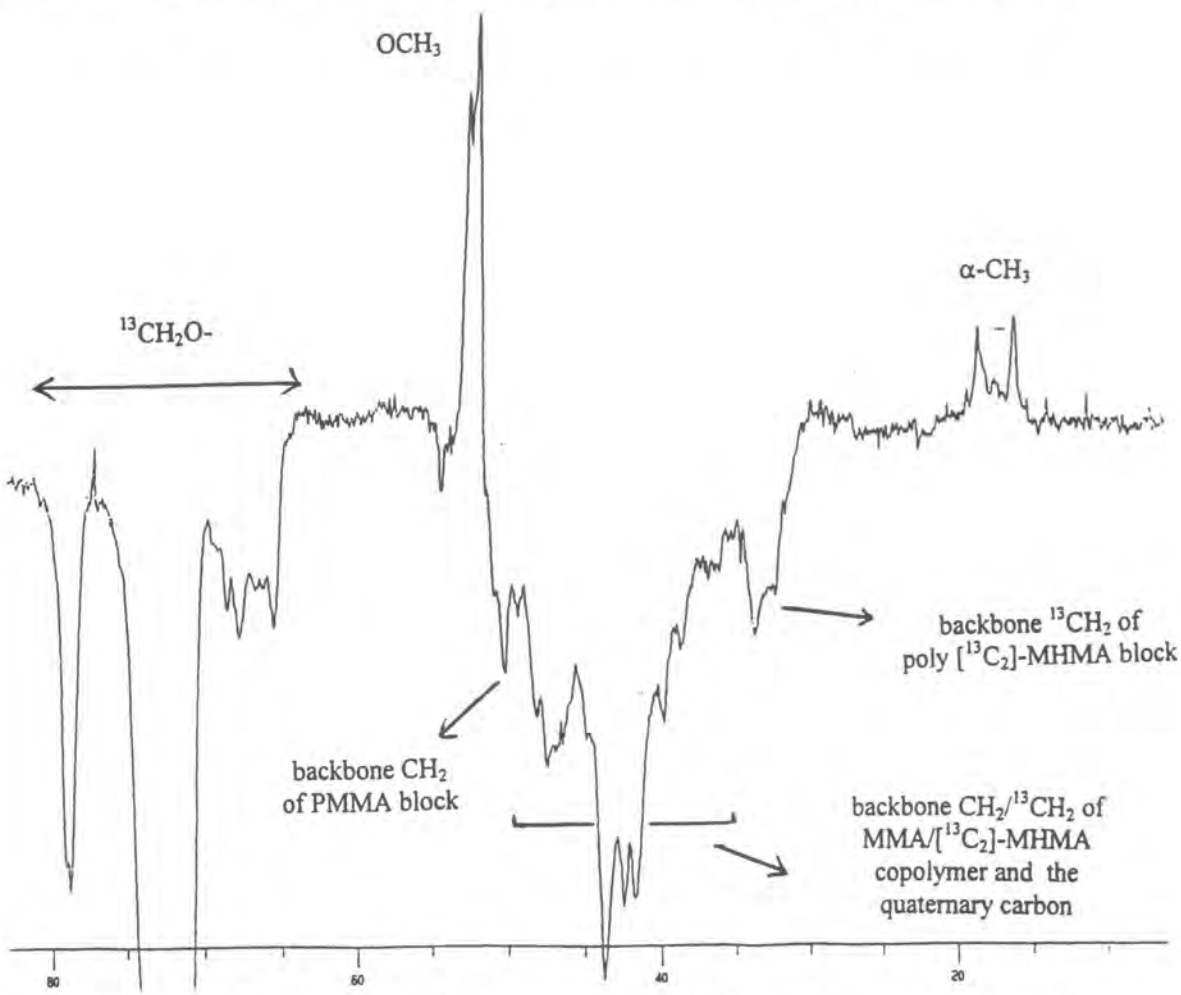


Figure 28 ^{13}C DEPT 135 NMR spectrum (75.5 MHz) of MMA/[$^{13}C_2$]-MHMA copolymer after lactonisation.

4.7.2 Molecular weight data

The molecular weights for the copolymers were obtained by GPC methods and are summarised in **Table 12**.

	MMA/MHMA		MMA/[$^{13}C_2$]-MHMA		MMA/[$^{2}H_4$]-MHMA	
Mw (untreated)	164000	PDI 2.6	108000	PDI 2.3	383000	PDI 3.9
Mn (untreated)	62000		46000		99000	
Mw (lactone)	27000	PDI 1.6	22000	PDI 1.7	58000	PDI 2.0
Mn (lactone)	17000		13000		29000	

Table 12 Molecular weight data of the copolymer before and after lactonisation

The GPC derived molecular weight data of the MMA/[$^{2}H_4$]-MHMA copolymer before lactonisation relative to MMA/MHMA or MMA/[$^{13}C_2$]-MHMA systems is very much higher. This observation is possibly due to reduced number of chain transfer reactions occurring in MMA/[$^{2}H_4$]-MHMA as a result of the stronger C-D bond.

The GPC elution times were longer for the lactonised copolymer suggesting a smaller hydrodynamic volume when compared with the corresponding untreated copolymer. GPC separates molecules according to their molecular size in solution, strictly the polymer molecules are not separated solely on the basis of molecular weight, but on the basis of hydrodynamic volume which is the volume a polymer molecule occupies in solution. The elution time will therefore be the same for two molecules with the same hydrodynamic volume even if their molecular weights differ. The consequence of the lactonised copolymer having a smaller hydrodynamic volume due to the cyclic groups

is that they stay within a pore for longer, their passage through the column being delayed and subsequently they elute slower.

The molecular weight obtained for the lactonised copolymers are significantly lower than the molecular weights observed before lactonisation. The GPC is calibrated using linear polystyrene polymer standards. The lactonised copolymer is cyclic and this may account for the lower molecular weight recorded.

4.7.3 DSC results

The MMA/MHMA and MMA/[$^2H_4$]-MHMA copolymers were then analysed by differential scanning calorimeter (DSC) by typically heating between 5-10 mg of the copolymer was from 50 °C to 300 °C under nitrogen, see **Table 13**.

	Tg before lactonisation	*Tg* lactone	Enthalpy of lactonisation
MMA/MHMA	102 °C	154 °C	110 Jg^{-1}
MMA/[$^2H_4$]-MHMA	119 °C	158 °C	96 Jg^{-1}

Table 13 Glass transition temperatures and enthalpy of lactonisation.

It is clear that lactonisation of the copolymer increases the *Tg* of the copolymer. The increase *Tg* is the direct result of chain stiffening due the introduction of cyclic groups into the polymer backbone of the lactonised copolymer.

Lactonisation can be achieved on heat treatment. An exotherm was observed on heating the unlactonised copolymers to above 200 °C. For the MMA/MHMA copolymer, the enthalpy of lactonisation was estimated to be of 110 Jg^{-1}, peaking at 232 °C. The enthalpy of lactonisation for the MMA/[$^2H_4$]-MHMA system was slightly lower and was estimated to be 96 Jg^{-1}, peaking at a slightly higher temperature of 244 °C. However, when the lactonised copolymers were re-heated no exotherm was observed suggesting that that lactonisation was complete on the first instance as reported previously.[4,3,6]

This study has shown that the MMA/MHMA copolymers contain small blocks of MMA and MHMA monomer units and has been able to securely assign the associated peaks using ^{13}C-NMR techniques. The optimum condition for the successful preparation of lactonised copolymer is in a toluene/methanol (1:1) solvent mixture using a few drops of conc. hydrochloric acid and DCM. The lactonisation is complete in 45 min on heating to 80 °C. In the ^{13}C-NMR spectrum of MMA/[$^{13}C_2$]-MHMA copolymer after lactonisation, there was no evidence of unreacted CH_2OH group, confirming that lactonisation was complete under these conditions.

4.8 References

1 T. Kashiwagi, A. Inaba, J. E. Brown, K. Hatada, T. Kitayama and E. Masuda, *Macromolecules,* 1986, **19,** 2160.

2 K. Hatada, T. Kitayama, K. Ute, Y. Terawaki and T. Yanagida, *Macromolecules,* 1997, **30**, 6754.

3 A. O. Kress, L. J. Mathias and G. Cei, *Macromolecules*, 1989, **22**, 537.

4 M. Ueda, T. Koyama, M. Mano and M. Yazawa, *J. Polym. Sci. A, Polym. Chem.,* 1989, **27**, 751.

5 M. C. Fernandez-Monreal, R. Cuervo and E. L. Madruga, *J. Polym. Sci. A,* 1992, **30**, 2313.

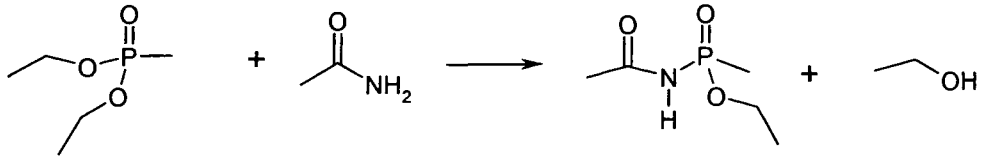
6 M. F. Fernandez-Garcia, E.L. Madruga, R. Cuervo-Rodriguez and M. C. Fernandez-Monreal, *Polymer*, **35**, 1994.

Chapter 5

Synthesis and polymerisation of phosphonate based methacrylate monomers

5.1 Introduction

There is a potential advantage in extending the application of fluorinated phosphonates into materials applications. For example, incorporating phosphonate esters on to moieties such as methyl methacrylate could confer fire retarding properties to the resultant materials or even lead to a new generation of ionic materials after ester hydrolysis. Conventionally, flame retardance is achieved through the use of additives, many of which can themselves present hazards in the form of emissions of toxic gases. There have been studies reported on the chemical modification of polymers to achieve flame retardance. For example, Ebdon *et al*[1] copolymerised diethyl vinylphosphonate (DEVP) with styrene, methyl methacrylate, acrylonitrile and acrylamide. They concluded that the incorporation of DEVP into polystyrene and polymethyl methacrylate has only a very small effect upon flame retardance as gauged from limiting oxygen index measurements. However, in the case of polyacrylonitrile, and notably with polyacrylamide, the effect of DEVP is much more significant. In polyacrylamide there is evidence for nitrogen-phosphorous synergism. They proposed that for DEVP-*co*-polyacrylamide, an increase in flame retardance may be aided by the formation of phosphoramide structures which serve to cross-link the polymer chains and maintain integrity during the early stages of combustion as shown in **Scheme 54**.



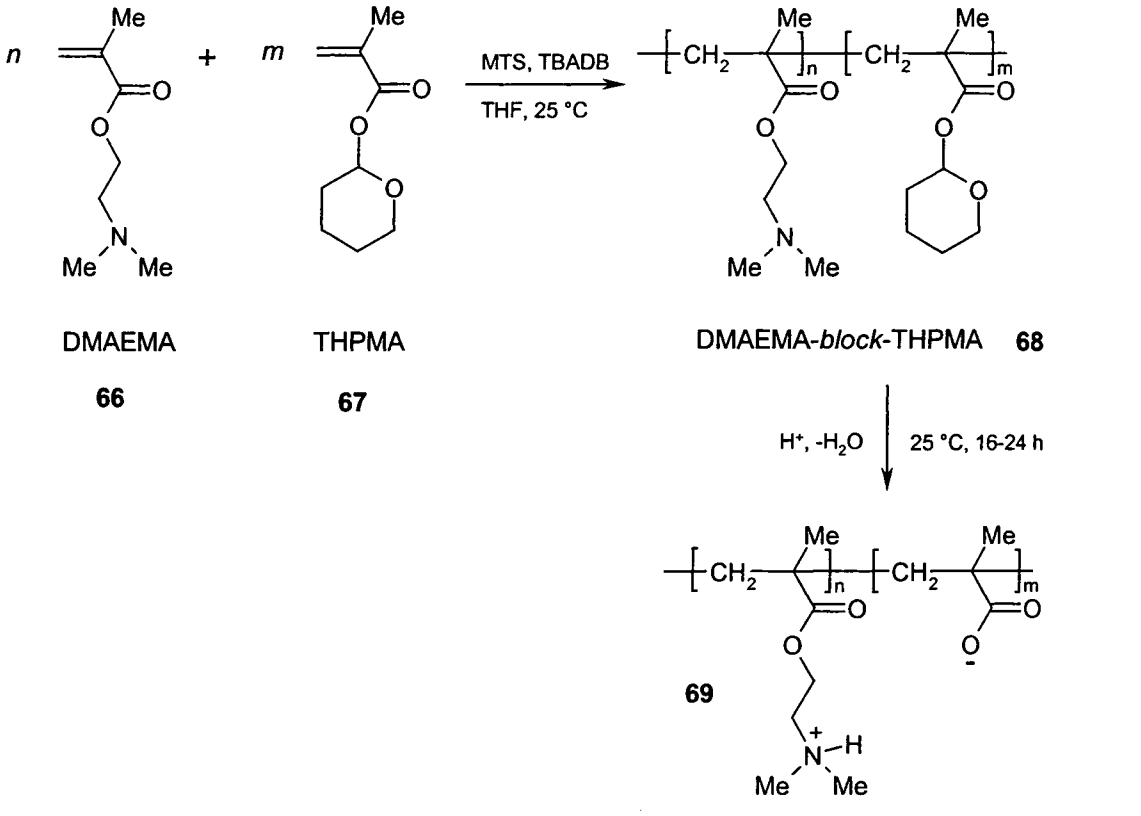
63 **64** **65**

Scheme 54

Recently Burton *et al*[2] prepared copolymers based on tetrafluoroethylene and perfluorovinylethers such as CF_2=$CFOCF_2P(O)(OC_2H_5)_2$ and also ter-fluoropolymers by the inclusion of perfluoro(propylvinyl)ether CF_2=$CFOC_3F_7$. The copolymers were hydrolysed to the corresponding phosphonic acids and were hot pressed to form films of thickness

0.10-0.14 mm. The films showed interesting properties such as proton conductivity and water absorption.

Further, Armes *et al*[3] obtained copolymers of 2-(dimethylamino)ethyl methacrylate (DMAEMA) and 2-tetrahydropyranyl methacrylate (THPMA) *via* group transfer polymerisation. The 2-tetrahydropyranyl protecting group was removed by acid hydrolysis to yield zwitterionic block copolymers as shown in **Scheme 55**. These were reported to undergo reversible temperature-induced micellation.

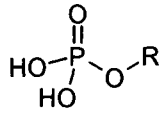


* 1-Methoxy-1-trimethylsiloxy-2-methyl-prop-1-ene (MTS) as the initiator.

* Tetrabutylammonium dibenzoate (TBADB) as the catalyst.

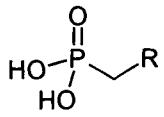
Scheme 55

Phosphonates have been used widely in bio-organic chemistry as the C-P bond is stable to hydrolysis from the phosphatase enzyme, unlike phosphates which are common in biological systems.[4] The pKa (second deprotonation) of a phosphate **70** and some phosphonate analogues, **71**, **72** and **73** are shown below. The pKa of the phosphate **70** is 6.4[5] as compared with 7.6 for the CH_2 phosphonate **71**. It is clear that the electronegativity of the oxygen is not matched by the CH_2 in the phosphonate, however the introduction of fluorine atoms onto the methylene group increases the acidity of the phosphonate due the electron withdrawing effect of the fluorine atoms.[6] Thus, the pKa of the CHF phosphonate is 6.5[7] and is similar to that of the phosphate. In a biological system, therefore, the hydrolytically stable CHF phosphonate emerges as an electronic mimic for the phosphates. A recent theoretical analysis has also indicated that the CHF phosphonate has a close electrostatic profile to the phosphate group.[8]



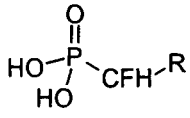
70

pKa = 6.4



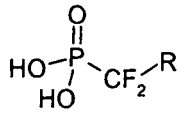
71

pKa = 7.6



72

pKa = 6.5

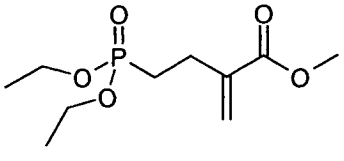


73

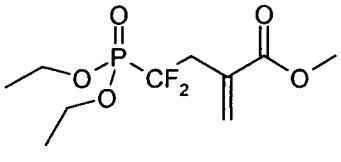
pKa = 5.4

5.2 Aims and objectives

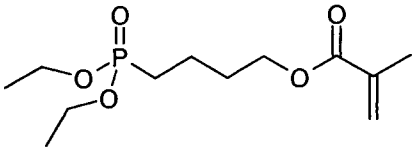
Phosphonate moieties introduced into copolymers appear to induce a level of flame retardance.[1] In addition, the introduction of fluorine atoms can confer improved thermal properties on a wide range of materials. It therefore appeared appropriate to investigate the incorporation of the $CF_2P(O)(OEt)_2$ group in PMMA type material. This latter functional group has the attraction of combining both the fluorine and phosphonate moieties. Four phosphonate based methacrylate monomers **74**, **75**, **76** and **77** were identified as synthetic targets. In order to assess the relative contributions of the effects of the fluorine and the phosphonate, preparation of the monomer analogues CH_2 and CF_2 were considered. Such polymers are also potential precursors for ionic materials.



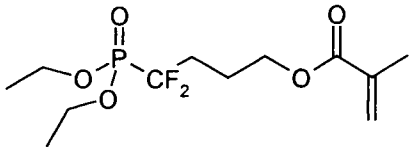
74



75



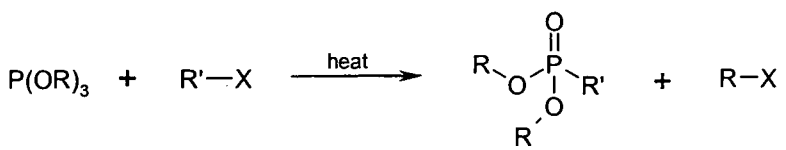
76



77

5.3 Review of methods available for the preparation of phosphonate esters

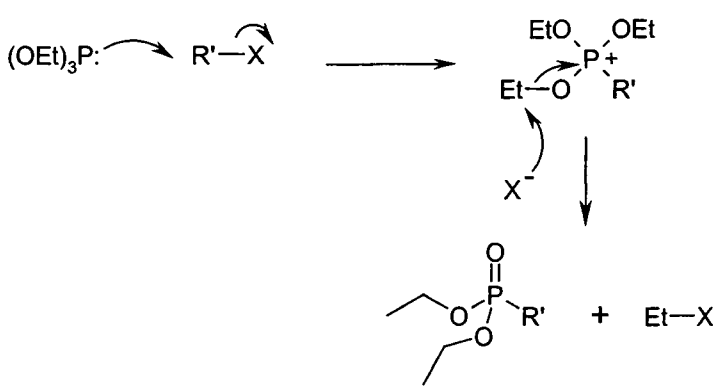
The Michaelis-Arbuzov reaction is one of the most versatile pathways for the introduction of carbon-phosphorous bonds from the reaction between alkyl/aryl phosphites and alkyl/acyl/aryl halides. The reaction was originally discovered by Michaelis[9] and later explored further by Arbuzov[10] and is now a commonly used method to prepare phosphonate esters, see **Scheme 56**.



R = alkyl, aryl
R' = alkyl, aryl, acyl
X = Cl, Br, I

Scheme 56

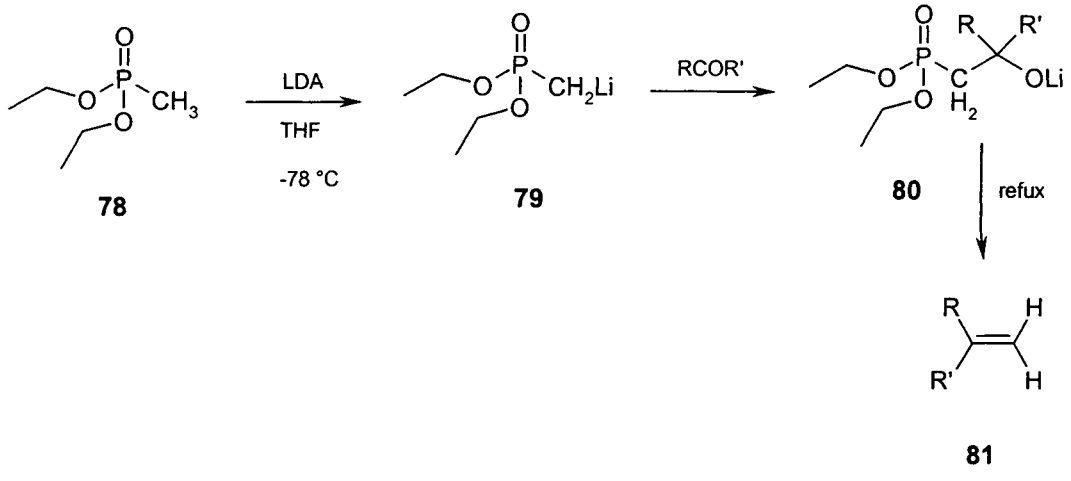
The reaction mechanism for the Michaelis-Arbuzov reaction is illustrated by the reaction between triethyl phosphite and an alkyl halide in **Scheme 57**. The lone pair of electrons of the phosphite attacks the alkyl halide resulting in the loss of halide ion. This is followed by attack of the halide on the ethyl group which results in the formation of the phosphorous-oxygen double bond and loss of ethyl halide to generate the phosphonate ester.



Scheme 57

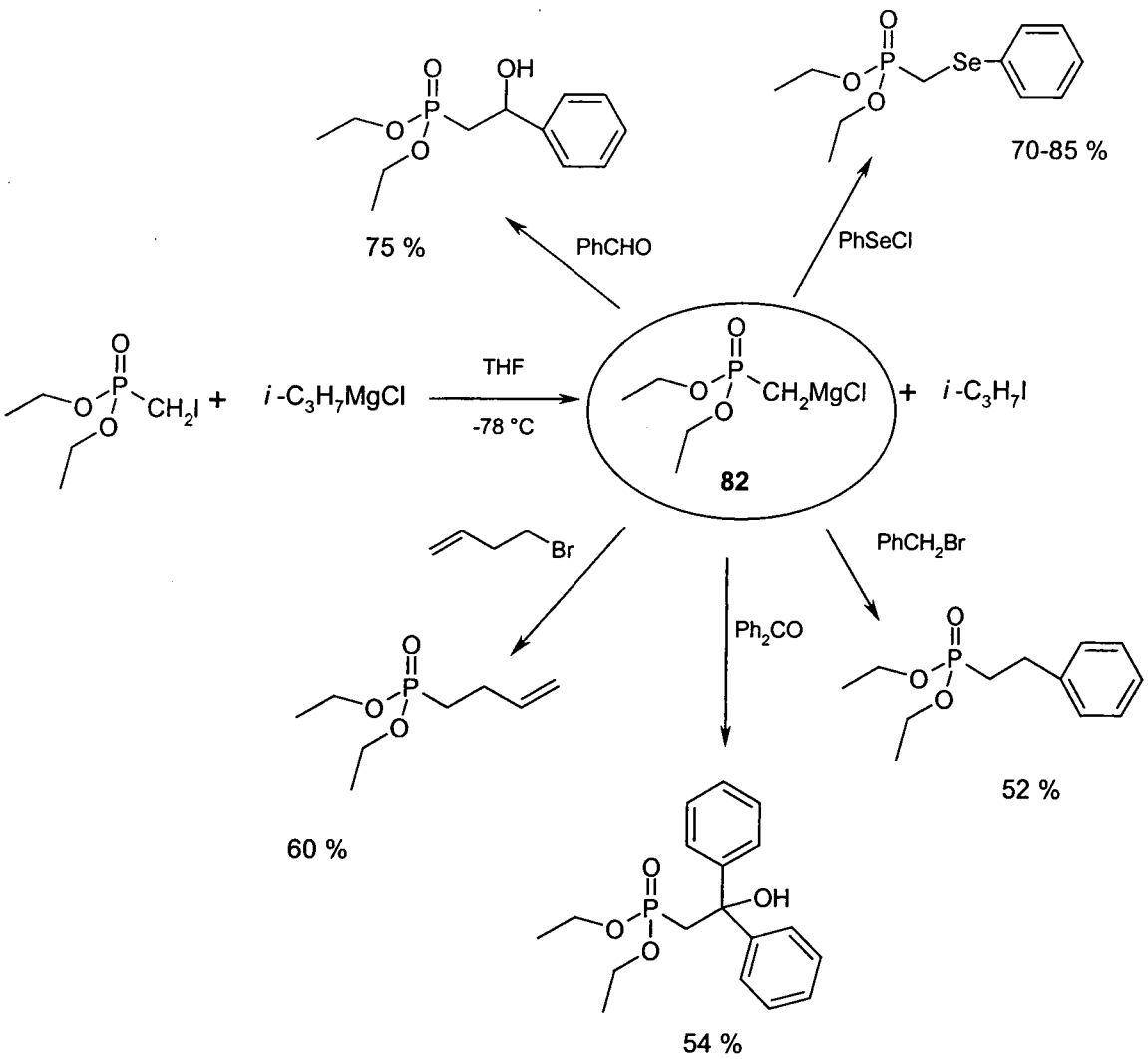
The phosphonate ester **78** when treated with a base such as LDA, generate anions which react with electrophilic aldehydes and ketones to undergo the Wadsworth-Emmons reaction

to give olefins **81**.[11] An example of such a reaction with a ketone is shown below in **Scheme 58.**



Scheme 58

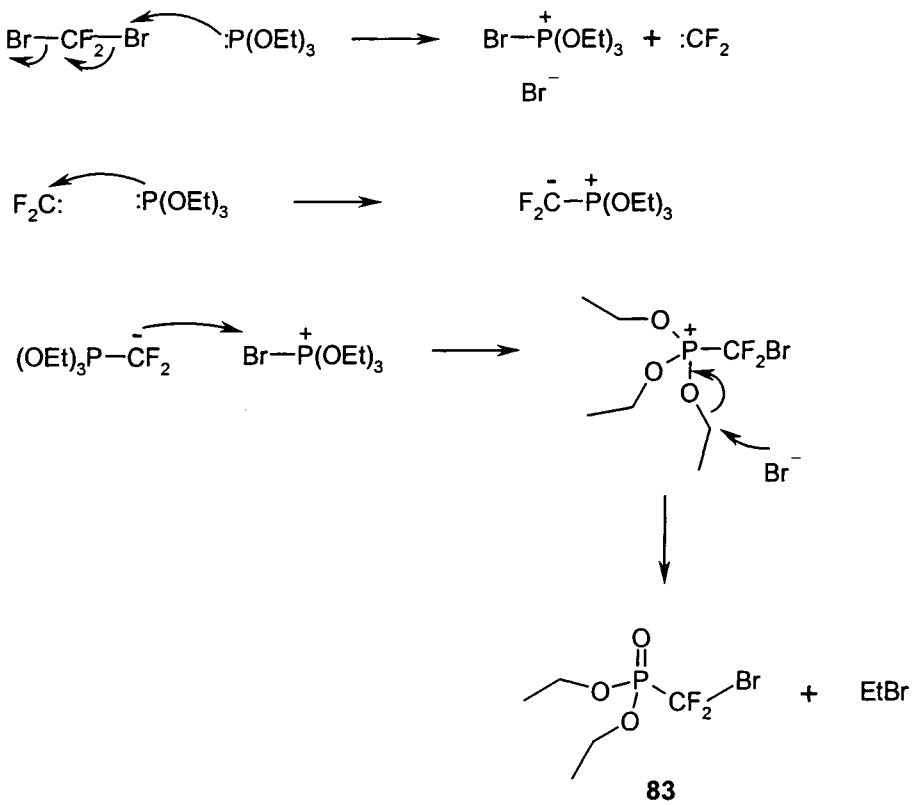
The phosphonate moiety can be coupled to aldehydes, ketones, alkyl and phenyl selenium halides through diethyl methylphosphonate magnesium chloride, see **Scheme 59**. This Grignard reagent **82** can be readily prepared by reacting diethyl iodomethylphosphonate and *i*-propyl magnesium chloride in THF at –78 °C.[12] Moderate to good yields were reported for the products generated by this route.


i-C3H7MgCl
THF
-78 °C
CH2I
CH2MgCl
i-C3H7I
82
PhCHO
75 %
PhSeCl
70-85 %
Br
60 %
Ph2CO
54 %
PhCH2Br
52 %
OH
Se

Scheme 59

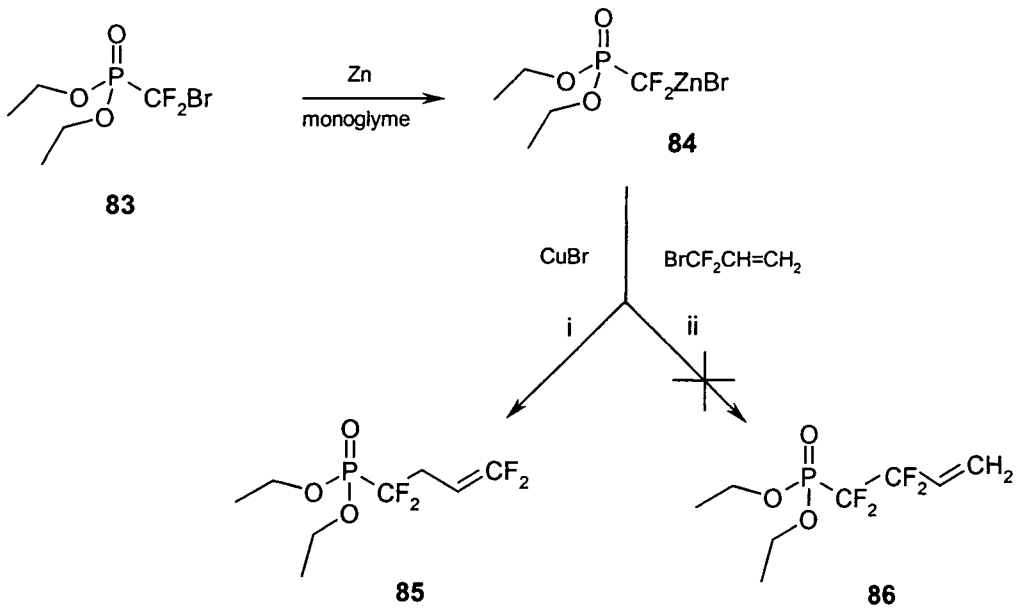
5.4 Review of methods available for the preparation of fluorinated phosphonates

The widely used Michaelis-Arbuzov reaction cannot be used to prepare 1,1-difluorophosphonates as fluorocarbons do not under go the necessary S_N2 type reaction. A convenient method to prepare such compounds is by reacting triethyl phosphite and dibromofluoromethane. This results in the formation of diethyl bromodifluoromethanephosphonate[13] as shown in **Scheme 60**. The mechanism superficially resembles the Michaelis-Arbuzov reaction, however, Burton[14] has proposed a more complex mechanism involving difluorocarbene.



Scheme 60

Burton[15] demonstrated that zinc treated diethyl bromodifluoromethanephosphonate readily reacts with a variety of allylic halides, under CuBr catalysis and a number of compounds were prepared to illustrate the versatility of this particular method. **Scheme 61** shows the reaction between the organozinc reagent **84** and 3-bromo-3,3-difluoropropene in which only one of the regioisomers, **85** was obtained because the mechanistic pathway involved is of the S_N2' type.



83 **84** **85** **86**

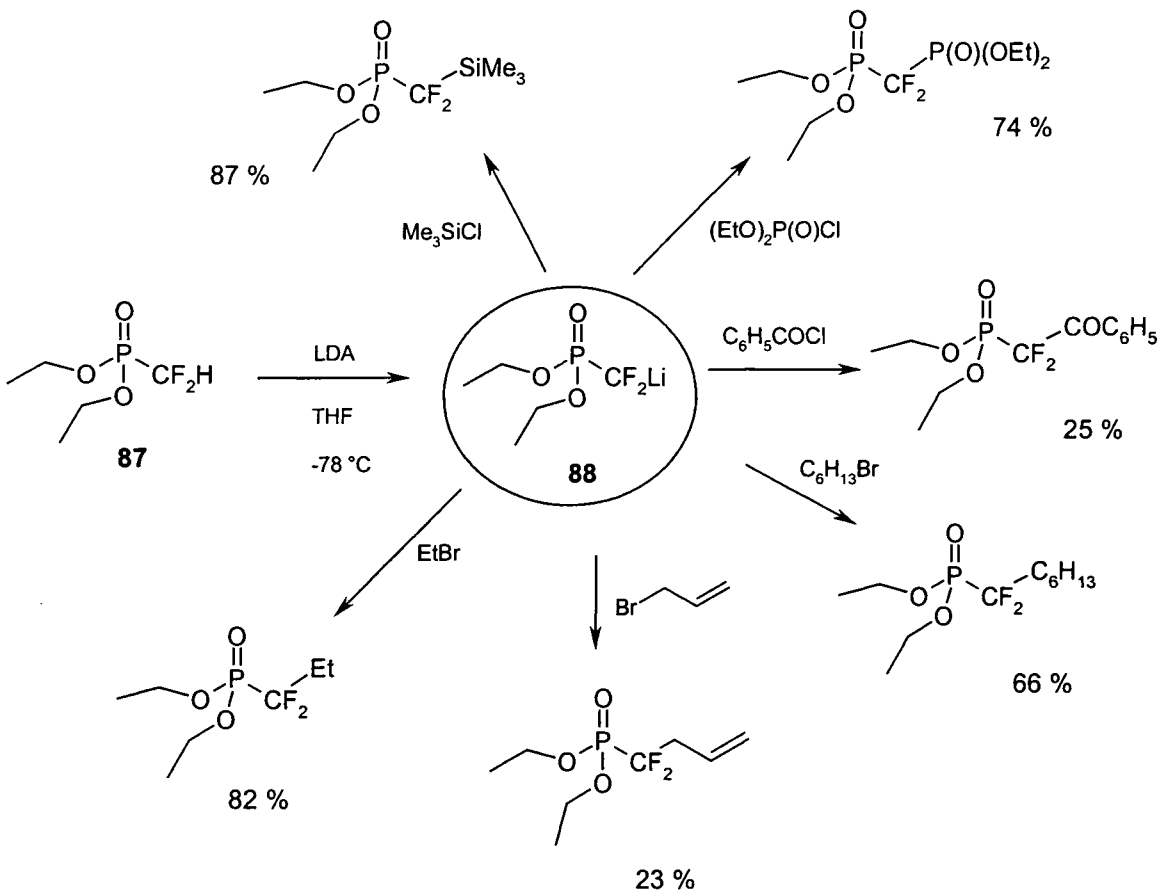
Scheme 61

Diethyl bromodifluoromethanephosphonate also reacts readily with cadmium metal to form stable complexes.[16]

$(EtO)_2P(O)CF_2CdBr$ $[(EtO)_2P(O)CF_2]_2Cd$

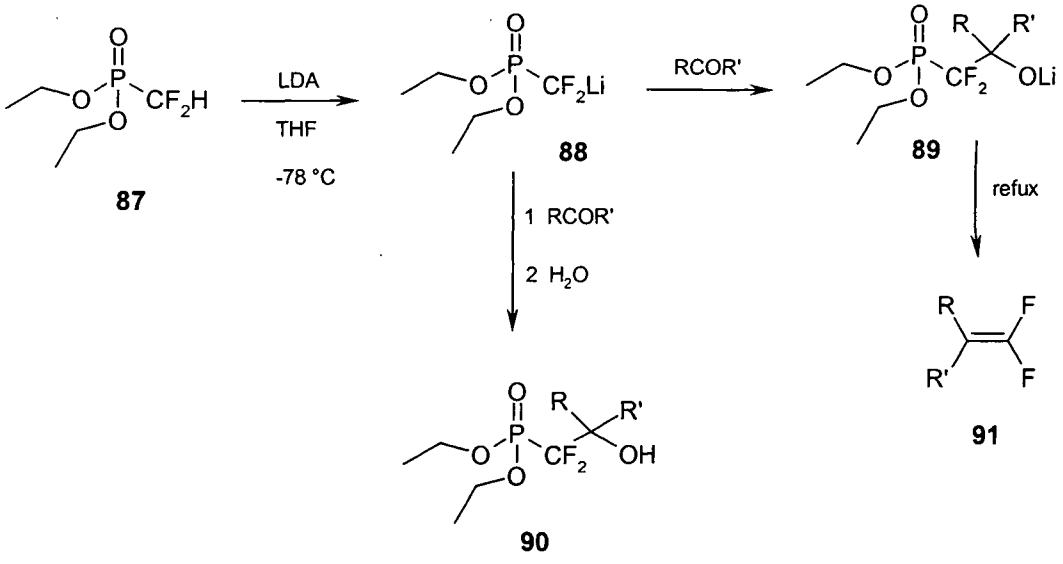
Depending on the solvent, the organocadmium reagent exhibits stability from just a few days to months. It reacts with a wide range of electrophiles such as allyl and acyl halides and is a convenient method to introduce the diethyl difluoromethylphosphonate moiety into organic molecules.

Alternatively, diethyl 1,1-difluorophosphonates are generally prepared by treating diethyl difluoromethylphosphonate **87** with lithium diisopropylamide and then reacting the anion **88** with an appropriate halide as shown in **Scheme 62**.[17]



Scheme 62

The diethyl difluoromethylphosphonate anions are also known to react readily with aldehydes and ketones. When aldehydes are treated with the phosphonate anions and the work up is carried out at room temperature, diethyl 2,2-difluoro-3-hydroxyalkylphosphonates **90** is generated. However, when aldehydes and ketones are reacted and the solution of the intermediary adduct heated, 1,1-difluoro olefin **91** are obtained *via* a Wadworth-Emmons reaction, see **Scheme 63**.

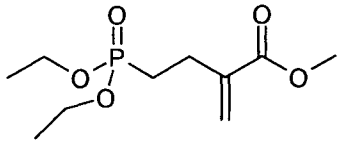


Scheme 63

5.5 Results and discussion

There are clearly a number of methods available for the preparation of both the non-fluorinated and fluorinated phosphonate esters. These synthetic methods have been explored during the preparation of the monomers **74**, **75**, **76** and **78**.

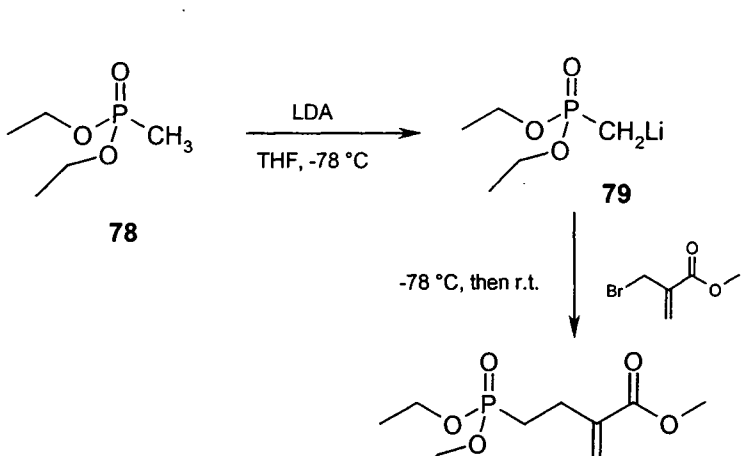
5.5.1 Synthesis of methyl 4-(diethoxyphosphinoyl)-2-methylenebutanoate 74



74

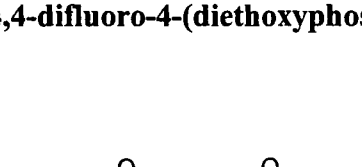
The synthetic strategy involved in preparing methyl 4-(diethoxyphosphinoyl)-2-methylenebutanoate **74** initially involved accessing the anion of diethyl methylphosphonate **78** as originally developed by Corey *et al* [11] and subsequently reacting it with methyl 2-(bromomethyl)acrylate. The anion was generated using *n*-BuLi at –78 °C and was then reacted with methyl 2-(bromomethyl)acrylate. However, this resulted in the formation of a

number of unidentifiable compounds presumably because this reagent is a strong nucleophilic base and therefore, our attention turned to LDA as an alternative base. LDA was prepared by the addition of *n*-BuLi to diisopropylamine and was then used to generate the anion of diethyl methylphosphonate. The target compound was obtained by eluting over silica gel (twice) in a very moderate yield (29 %) as shown in **Scheme 64**.



Scheme 64

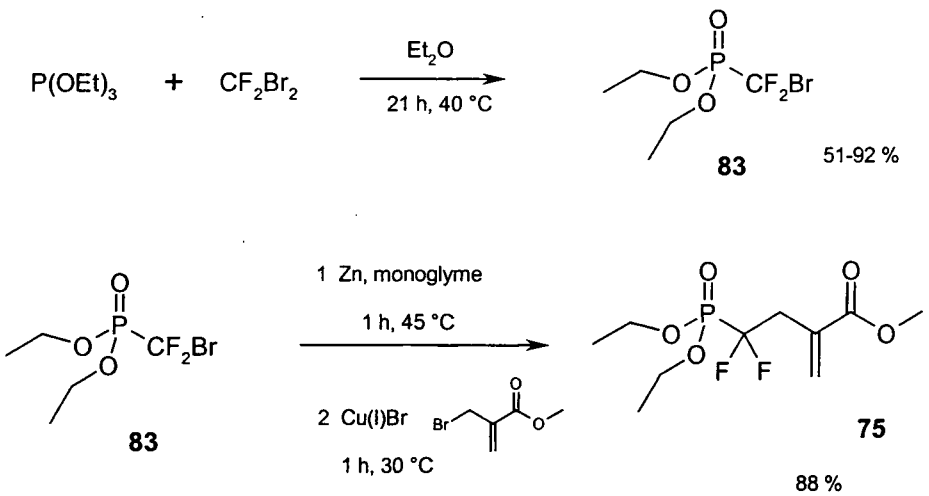
5.5.2 Synthesis of methyl 4,4-difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoate 75



75

The preparation of methyl 4,4-difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoate was carried out by using the methodology developed by Burton *et al*[13]. This has recently been explored by Campbell *et al*[18] to prepare **75** and a number of related compounds.

The first stage towards the preparation of the target was to generate diethyl bromodifluoromethylphosphonate **83** as shown in **Scheme 65**.[13]

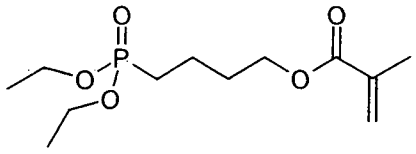


Scheme 65

This was prepared by mixing triethyl phosphite and dibromodifluoromethane. Due to the low boiling point of dibromodifluoromethane (24 °C), it was necessary to have an excess of this material at the beginning of the reaction. Further quantities were also added during the course of the reaction in order to compensate for evaporation during reflux in ether. The product was obtained in an excellent yield of 92 %.

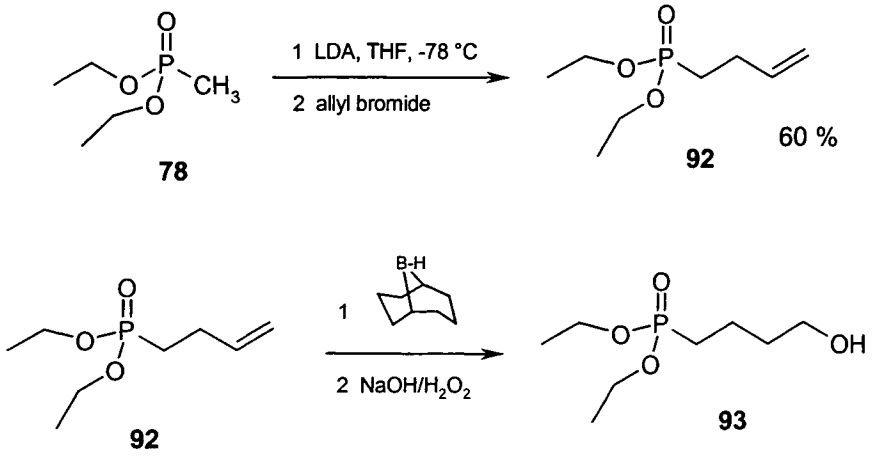
The diethyl bromodifluoromethylphosphonate prepared was then treated with acid washed zinc for 19 h at room temperature to generate the organozinc reagent. [15] However, it was later discovered that heating the mixture to 45 °C in thoroughly acid washed zinc yielded the product within an hour. The formation of the reagent could be detected by ^{19}F-NMR by an upfield shift of the fluorine signal (doublet) from -62 ppm to -129 ppm. This organozinc reagent readily reacted with methyl 2-(bromomethyl)acrylate in the presence of catalytic amounts of Cu(I)Br to give the title compound in good yield (88 %) as shown in **Scheme 65**. Purification over silica gel gave the required monomer in high purity (>98 %) and this material was prepared in several gram batches and was used for polymerisation studies.

5.5.3 Synthesis of 4-(diethylphosphinoyl)butyl methacrylate 76



76

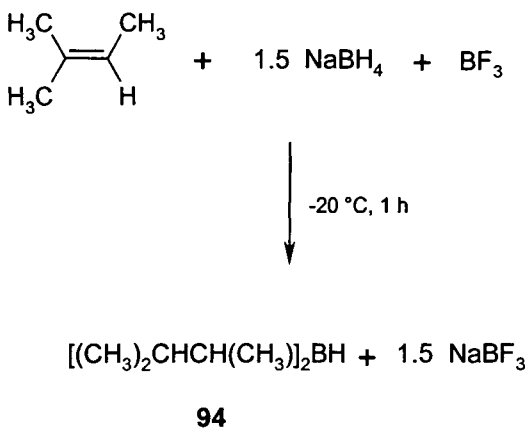
An important intermediate for our preparation of diethyl 4-(diethylphosphinoyl)butyl methacrylate **76** was diethyl but-3-enylphosphonate **92**. Preparation of **92** was achieved by treating diethyl methylphosphonate with LDA and then reacting the resultant anion allyl bromide as shown in **Scheme 66**. At the end of the reaction, unreacted diethyl methylphosphonate was removed by fractional distillation to give **92** in a moderate yield (60 %).



Scheme 66

Attempts were then made to hydroborate **92** using 9-borabicyclo[3.3.1] nonane (9-BBN) and oxidise the organoborane formed using alkaline hydrogen peroxide to convert the terminal olefin into a primary alcohol.[19] However, the use of this reagent did not generate the required target and it proved necessary to find an alternative hydroborating reagent.

In 1960 Brown *et al*[20] explored various hydroborating agents and reported that disiamylborane **94** readily allowed the preparation of primary alcohols from terminal olefins. This reagent was found to be far superior to the generally used diboranes and showed greater selectivity between terminal and internal double bonds. Preparation of **94** was carried out by treating 2-methyl-2-butene with sodium borohydride followed by the reaction with boron trifluoride etherate in THF at –20 °C, see **Scheme 67**.



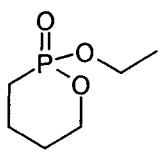
Scheme 67

The disiamylborane generated was then reacted *in-situ* with diethyl but-3-enephosphonate. By monitoring the reaction by TLC it was possible to detect the formation of the organoborane. Oxidation was carried out with a mixture of hydrogen peroxide and sodium hydroxide solution to give diethyl 4-hydroxybutylphosphonate **93** in a good yield (270 mg, 62 %).

Esterfication of the material generated was initially carried out with methacryloyl chloride in a solution of pyridine. The reaction was found to be very slow, typically requiring 6-12 h and generally resulting in poor yield of **76**. The reaction was, however, successful when carried out in triethylamine using a catalytic amount of *N,N*-dimethylaminopyridine.[21,22] Using this method, 110 mg (83 %) of the required monomer was prepared.

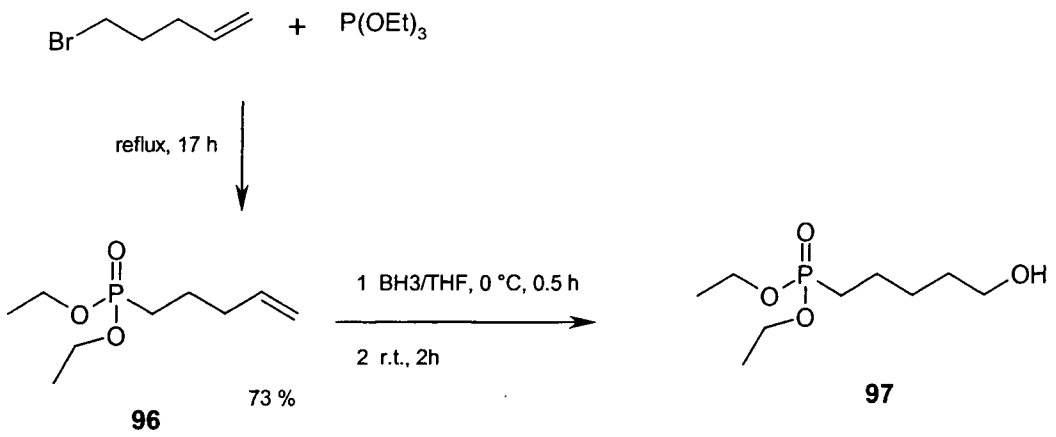
Attempts were then made to scale up the reaction on a larger scale to prepare diethyl 4-hydroxybutylphosphonate **93**. Although this compound had previously been prepared successfully, further attempts to generate this material on a bigger scale proved unsuccessful. An alternative method to prepare **93** was explored.

Recently, it was reported that allyl phosphonates can be hydroborated using a BH_3/THF complex[23] and that diethyl 4-hydroxybutylphosphonate could be prepared in a moderate yield of 30%. However, yields for longer chains were typically 90 % or greater. The poor yield of diethyl 4-hydroxybutylphosphonate may be due to the formation of stable 6-membered cyclic compound **95**, formed during the oxidation step.[24]



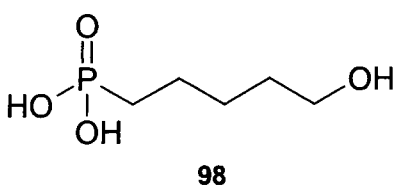
95

To circumvent the problem of possible cyclisation, diethyl pent-4-enylphosphonate **96** was identified as a suitable alternative. Preparation of this compound was relatively straight forward and was achieved by refluxing 5-bromopent-1-ene with an excess of triethyl phosphite as shown in **Scheme 68**. Vacuum distillation gave compound **96** in a good yield of 73 %.



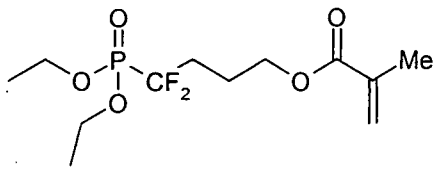
Scheme 68

The resultant product was treated with BH_3/THF and was oxidised with $NaBO_3$. The product was identified to be the phosphonic acid derivative **98** formed by hydrolysis. Using this method the intended target compound **97** was not possible to prepare.



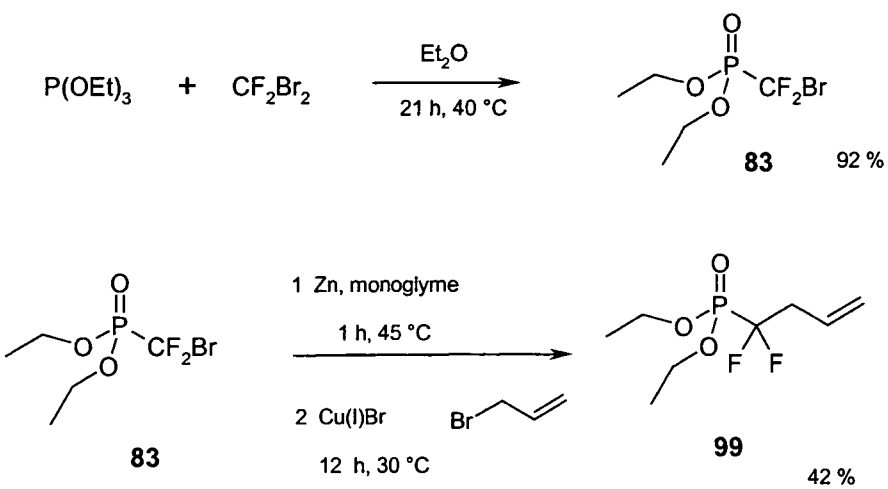
98

5.5.4 Synthesis of 4-(diethylphosphinoyl) 1,1-difluorobutyl methacrylate 77



77

The first stage towards the preparation of 4-(diethylphosphinoyl) 1,1-difluorobutyl methacrylate was to prepare diethyl bromodifluoromethylphosphonate as described earlier.[13] The resultant diethyl bromodifluoromethylphosphonate was treated with zinc and reacted with allyl bromide using Cu(I)Br as the catalyst.[15] On distillation, diethyl 1,1-difluorobut-3-enylphosphonate **99** was obtained in a moderate yield of 42 %, see **Scheme 69**.

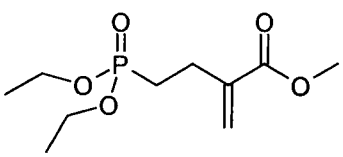


Scheme 69

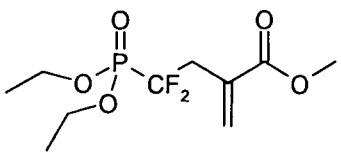
Attempts were then made to convert the diethyl 1,1-difluorobut-3-enylphosphonate using 9-BBN and disiamylborane as hydroborating agents to the corresponding primary alcohol as described earlier. Both reagents failed to give the desired product and therefore it was not possible to prepare monomer **77** for polymerisation studies.

5.6 Polymerisation methods

Of the four initially identified monomers, three were successfully prepared. With these target monomers **74**, **75** and **76** in hand it became important to explore their polymerisation. All of the free radical polymerisations were conducted in toluene at 80 °C using AIBN as the initiator at 0.5 wt.%. Anionic polymerisations were carried out in toluene at –50 °C using 1.6 M *n*-BuLi as the initiator. At the end of the polymerisation the polymer was recovered by precipitating into hexane and dried to constant weight (80 °C).



74



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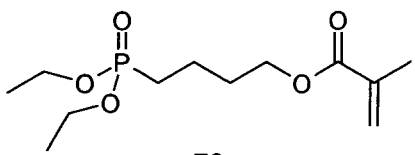
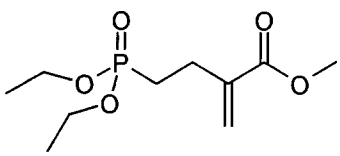


76

5.6.1 Polymerisation of methyl 4-(diethoxyphosphinoyl)-2-methylenebutanoate 74



74

Free radical polymerisations

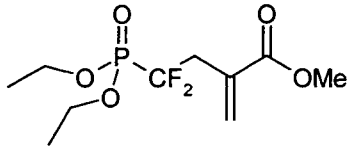
In order to establish a working experimental procedure, a control polymerisation of MMA (100 mg) was carried out initially. In this case a polymer of Mw = 10032 and Mn = 3415; PDI=2.94 was obtained as shown in **Table 14**. However under similar conditions monomer **74** failed to polymerise. Only starting material was recovered at the end of the polymerisation.

Monomer	Duration	Yield	Molecular weight
MMA (100 mg)	18 h	80 mg, 80 %	Mw = 10032 Mn = 3415
Monomer **74** (100 mg)	18 h	-	-

Table 14 Results of the free radical polymerisation.

However, it was discovered somewhat to our surprise that this monomer oligomerised on storage, to give a polymer with Mw = 4955 and Mn = 1000. The molecular weight distribution was very broad with a PDI of 4.96. The polymer was fractionated to give a polymer of with Mw = 815, Mn = 880 and PDI 1.08.

5.6.2 Polymerisation of methyl 4,4-difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoate 75



75

Free radical polymerisations

Initially MMA was polymerised as a control and a polymer of molecular weight Mw = 23550 and Mn = 10200; PDI=2.31 was obtained see **Table 15**.

Monomer	Duration	Yield	Molecular weight
MMA (1 g)	4 h	0.88 g, 88 %	Mw = 23550 Mn = 10200
MMA (0.9 g) Monomer **75** (0.1g)	4 h	0.21 g, 21 %	Mw = 14330 Mn = 7651
Monomer **75**	24 h	-	-

Table 15 Results of the free radical polymerisations.

The next step was to copolymerise MMA with methyl 4,4-difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoate under similar conditions. This resulted in a material with a lower molecular weight of Mw = 14330 and Mn = 7651; PDI=1.87 when compared with MMA homopolymer. The copolymer was then analysed by ^{19}F-NMR to assess the level of incorporation of **75**. The absence of fluorine signals in the ^{19}F-NMR indicated that copolymerisation had not taken place and this material was in fact PMMA.

Attempts to generate a homopolymer of **75** resulted in a viscous solution at the end of the polymerisation. Precipitation into hexane gave a milky white emulsion which was concentrated under reduced pressure. ^{1}H and ^{19}F-NMR analysis indicated that the monomer was substantially intact and had not polymerised.

Carius tube free radical polymerisations

In an attempt to generate a copolymer of MMA (0.8 g) and **75** (0.2 g) under more forcing conditions, the mixtures were placed in a Carius tube with AIBN and heated to 140 °C for 15 h. The product was a highly viscous liquid. Dissolving in toluene and precipitating in hexane gave a white polymer. However, once again there were no fluorine signals in the ^{19}F-NMR indicating that **75** had not become incorporated into the material and that this polymer was PMMA.

An attempt was then made to obtain a homopolymer of **75** under these conditions. Treatment of **75** in the presence of AIBN, at 140 °C in a Carius for 24 h resulted in a viscous liquid. However, again no polymer was obtained on precipitation. It was therefore concluded that this monomer does not polymerise under radical conditions.

Anionic polymerisations

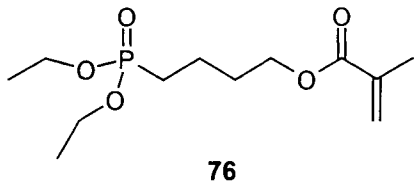
Following the failure of monomer **75** to polymerise under radical conditions, anionic polymerisation was explored. Again a model protocol was established where MMA was polymerised using n-BuLi as the initiator for 16 hrs under nitrogen. The polymer was recovered in excellent yield (93 %) as shown in **Table 16**

Monomer	Duration	Yield
MMA (1 g)	16 h	0.93 g, 93 %
MMA (0.5 g) Monomer **75** (0.5 g)	16 h	-

Table 16 Results of the anionic polymerisations.

An experiment was then conducted where MMA (0.5 g) and **75** (0.5 g) were copolymerised under similar conditions. However, on precipitation into hexane, no polymer could be recovered. This anionic polymerisation failed.

5.6.3 Polymerisation of 4-(diethylphosphinoyl)butyl methacrylate



76

4-(diethylphosphinoyl)butyl methacrylate proved a difficult target to prepare. Efforts to generate this material resulted in only a small quantity of material and this was used to explore the polymerisation reactions. Initially, MMA was subjected to polymerisation and a polymer of Mw = 12158, Mn = 24563; PDI = 2.0 was obtained as shown in **Table 17** Attempts to polymerise **76** (110 mg) were unsuccessful and the ^{1}H-NMR analysis of the material recovered indicated that the monomer was substantially intact and no polymerisation had taken place.

Monomer	Duration	Yield	Molecular weight
MMA (110 mg)	20 h	98 mg, 80 %	Mw = 12158 Mn = 24563
Monomer **76** (110 mg)	20 h	-	-

Table 17 Results of the free radical polymerisation.

Anionic polymerisation

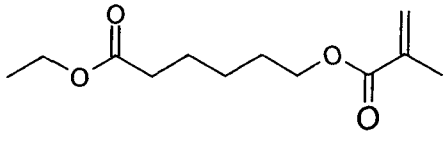
Iniatially MMA was polymerised using *n*-BuLi. This resulted in a polymer of Mw = 8717, Mn = 1511, whereas, attempts to polymerise **76** failed to give a polymer, see **Table 18**. However, much more encouraging results were obtained upon copolymerisation with MMA. ^{1}H-NMR of the copolymer indicated that the double bonds had almost disappeared. The GPC of the copolymer had a broad bimodal distribution and the ^{31}P-NMR had two

significantly different signals. A singlet at 32 ppm was consistent with the presence of the original monomer and the more predominant signal at 25 ppm was attributed to the copolymer.

Monomer	Duration	Yield	Molecular weight.
MMA (50 mg)	18 h	22 mg, 44 %	Mw = 8717 Mn = 1511
76 (50 mg)	18 h	-	-
MMA (50 mg) **76** (50 mg)	18 h	36 mg, 36 %	Mw = 3693 Mn = 1072

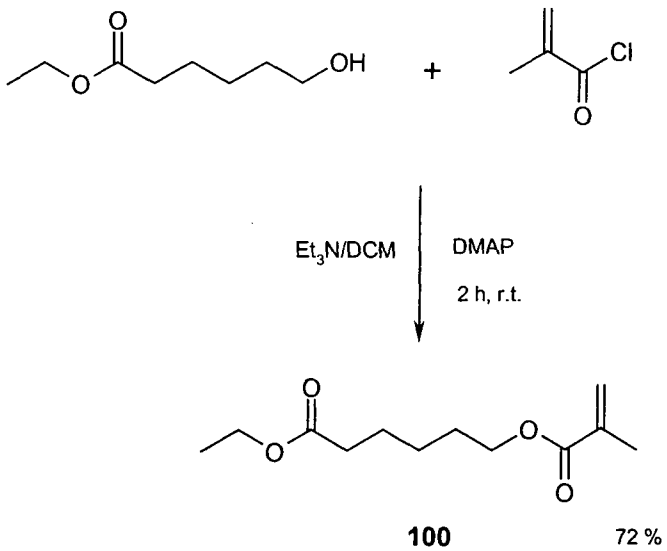
Table 18 Results of the anionic polymerisations.

5.6.4 Synthesis and polymerisation of ethyl 6-hydroxyhexanoate methacrylate 100



100

Due to the difficulty in generally polymerising the phosphonate based methacrylate monomers, it was important to assess the influence of the phosphonate group on the polymerisation. In view of this, ethyl 6-hydroxyhexanoate methacrylate **100** was prepared. The synthesis of **100** proved to be a relatively straight forward process. Ethyl 6-hydroxyhexanoate is a readily available compound and was coupled with methacryloyl chloride in triethyl amine/DCM mixture using DMAP as a catalyst, see **Scheme 70**. Distillation gave the desired product in a 72 % yield. In the first instance about 2 g of this material was prepared and the reaction was later scaled up to prepare 10 g of the monomer.



Scheme 70

Free radical polymerisations

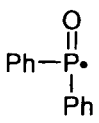
Initially, MMA was polymerised as a control and a polymer of Mw = 141096 and Mn = 66850 was obtained, see **Table 19**. Polymerisation of **100** resulted in a polymer of higher molecular weight, Mw = 299131 and Mn 100265.

Monomer	Duration	Yield	Molecular weight
MMA (5 g)	15 h	4.7 g, 94 %	Mw = 141096, Mn = 66850
100 (5 g)	15 h	4.4 g, 88 %	Mw = 299132, Mn = 100265

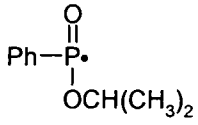
Table 19 Results of the free radical polymerisation

5.7 Discussion and conclusion

Polymerisation of methacrylate based phosphonate monomers **74**, **75** and **76** has in general been difficult perhaps due to phosphorus being a radical acceptor. There is some evidence in the literature that phosphinyl radicals **101**, **102**, **103** and **104** may be formed as a result of photodecomposition of acyl phosphinates or acyl phosphine[25,26,27] or through hydrogen abstraction from the phosphine oxide.[28]



101



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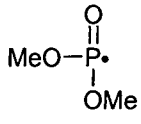

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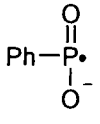

104

Monomer **74,** however, oligomerised on storage to form a viscous liquid (Mn = 1000) whilst **100** polymerised. Polymerisation of **100** where the monomer bears no phosphonate moiety indicates that phosphorous may play an important part in retarding the polymerisation process.

Polymerisations carried out using *n*-BuLi as the initiator may be complicated by nucleophilic attack to the carbonyl group. The initiator may also react with the ethyl group of the phosphonate moiety. These reactions would lead to the loss of the initiator and suppress the ability of the monomers to polymerise. Success, however, was achieved in generating a co-oligomer of **76** and MMA (Mn =1072).

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Chapter 6

Experimental

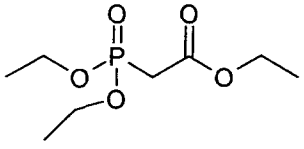
6.1 General methods

NMR spectra were recorded on Bruker AC-250 (250.13 MHz) and Varian Inova (499.78 MHz), VXR-400S (399.96 MHz), Unity (299.91 MHz) and Mercury (199.99 MHz) spectrometers in $CDCl_3$ solution unless otherwise stated, using the deuterated solvent as the lock and as reference. Deuterium NMR spectra were recorded on Unity (46.04 MHz) spectrometer in $CDCl_3$ solution. Infra red spectra were recorded with absorption values in cm^{-1}on a Perkin Elmer 257 Spectrometer as a neat film between NaBr discs. GCMS analysis was carried out on a VG Trio 1000 spectrometer (under EI or ammonia gas CI conditions) equipped with a HPI capillary column (25 m long, 0.22 mm i.d., 0.2 μm film thickness) connected to a H.P 5890 series II oven. Mass spectra were recorded with Micromass Autospec spectrometer (at low resolution, under EI or ammonia gas CI conditions) or by EPSRC National Mass Spectrometry Service at Swansea, with a Finnigan MAT 900 XLT (at high resolution, under EI or ammonia gas CI). Elemental analysis of carbon and hydrogen was carried out on a CE-440 elemental analyser. Glass transition temperatures and enthalpies of lactonisation were recorded on a Mettler Toledo Star^e System differential scanning calorimeter. GPC was carried out using a Waters 590 Series chromatograhic equipment, with three 300 mm x 7.7 mm Polymer Laboratories (PL) columns arranged in series and packed with polystyrene gel with particle size 5 μm and pore size 100, 10^3 and 10^5 Å. A Waters 401 differential refractometer was used as a detector. The polymer samples were dissolved in chloroform with toluene as the flow marker. The molecular weight averages were computed using PL software and calibrated against seven commercial polystyrene standards of molecular weight, 1030000, 777000, 435500, 127000, 47000, 3250, 162.

All the glassware was dried in an oven (125 °C) and cooled in a dry atmosphere of nitrogen or heated using a hot air gun to about 200 °C under high vacuum (<0.1 mbar). Reaction solvents were dried and freshly distilled prior to use. Petrol refers to the fraction boiling between 40-60 °C. Thin layer chromatography (TLC) was carried out using Merck, Kieselgel 60, F_{254} aluminium with glass backed plates. The plates were visualised using 254 or 366 nm wavelength UV lamp or permanganate, phosphomolybdic acid or iodine stains. Column chromatography was carried out over silica gel Merck, Kieselgel 60, 230-400 mesh.

6.2 Experimental procedures

6.2.1 Triethyl phosphonoacetate[1] 35



Triethyl phosphite (10 g, 60.9 mmol) and ethyl 2-bromoacetate (10.05 g, 60.9 mmol) were heated at 90 °C for 2 h. The mixture was concentrated under reduced pressure to remove ethyl bromide and vacuum distilled (68 °C/0.05 mbar, lit.[1] 90-93 °C/0.3 Torr) to give the title compound (11.06 g, 82 %) as a colourless oil.

^{1}H-NMR (400.0 MHz) δ 1.29 (3H, t, $^3J_{H\text{-}H}$ = 7.0 Hz, C(O)OCH$_2$C**H**$_3$), 1. 37 (6H, t, $^3J_{H\text{-}H}$ = 7.1 Hz, P(O)OCH$_2$C**H**$_3$), 2.96 (2H, d, $^2J_{H\text{-}P}$ = 21.6 Hz, C**H**$_2$), 4.19 (6H, m, OC**H**$_2$CH$_3$).

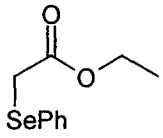
^{13}C-NMR (100.6 MHz) δ 14.1 (1C, s, C(O)OCH$_2$**C**H$_3$), 16.3 (2C, d, $^3J_{C\text{-}P}$ = 6.1 Hz, P(O)OCH$_2$**C**H$_3$), 34.35 (1C, d, $^1J_{C\text{-}P}$ = 134.3 Hz, **C**H$_2$), 61.6 (1C, s, C(O)O**C**H$_2$CH$_3$), 62.68 (2C, d, $^2J_{C\text{-}P}$ = 6.03 Hz, P(O)O**C**H$_2$CH$_3$), 165.8 (1C, d, $^2J_{C\text{-}P}$ = 6.1 Hz, **C**=O).

^{31}P-NMR (161.9 MHz) δ 20.9 (1P, s, **P**=O).

υ (cm^{-1}) 2984, 1738, 1271 and 1028.

m/z (CI) 242 ([M+NH$_4$]$^+$ 32.2 %), 225 ([M+H]$^+$ 100 %)

6.2.2 Ethyl α-selenophenylacetate[2] 30



Sodium borohydride (0.49 g, 13.0 mmol) was added to a solution of diphenyl diselenide (2.0 g, 6.4 mmol) in ethanol (35 ml). When the bright yellow solution turned colourless (~30 min), ethyl 2-bromoacetate (11.3 mmol, 1.3 ml) was added and the mixture was

heated under reflux for 2 h. The mixture was concentrated under reduced pressure, washed with water (3 x 20 ml) and extracted into ethyl acetate (3 x 20 ml). The organic extracts were combined, washed with sodium carbonate (3 x 15 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Vacuum distillation (75-80 °C/0.03, lit.[2] 77-80 °C/0.025 mbar) gave the title compound (1.38 g, 50 %).

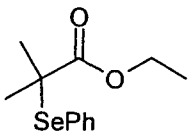
^{1}H-NMR (299.9 MHz) δ 1.19 (3H, t, $^3J_{H\text{-}H}$ = 7.2 Hz, $OCH_2\mathbf{CH_3}$), 3.5 (2H, s, $\mathbf{CH_2}$), 4.12 (q, $^3J_{H\text{-}H}$ = 6.9, $O\mathbf{CH_2}CH_3$), 7.28-7.58 (5H, m, $C_6\mathbf{H_5}$).

^{13}C-NMR (75.4 MHz) δ 14.3 (1C, s, $OCH_2\mathbf{C}H_3$), 27.9 (1C, s, $\mathbf{C}H_2SePh$), 61.6 (1C, s, $O\mathbf{C}H_2CH_3$), 127.9-133.7 (6C, s, $\mathbf{C}_6H_5$), 171.1 (1C, s, **C**=O).

υ (cm^{-1}) 2908, 1729, 1476, 1437, 1261 and 1107.

m/z (EI) 244 ($[M+H]^+$ 100 %), 214 (M^+-OEt, 3.3 %), 170 (M^+-C(O)OEt, 6.9 %), 156 (M^+-$C(O)OEtCH_2$, 9.3 %), 77 (M^+-$C(O)OEtCH_2Se$, 31.8 %).

6.2.3 Ethyl α-selenophenylisobutyrate[2] 31



n-BuLi (1.18 ml, 1.6 M, 1.9 mmol,) was added slowly to a solution of *n*-isopropylcyclohexylamine (0.33 ml, 2.0 mmol) in THF (2 ml) at -78 °C and stirred for 15 min. Ethyl isobutyrate (0.32 ml, 1.7 mmol) was added to the reaction and stirred for 15 min followed by the dropwise addition of a solution of phenylselenyl chloride (0.36 g, 1.9 mmol) in THF (2 ml). The mixture was stirred at this temperature for 90 min, poured into ammonium chloride solution (30 ml) and was then extracted into ethyl acetate (3 x 25 ml). The organic extracts were washed with 1 M HCl (15 ml) and thus a saturated solution of $NaHCO_3$ (15 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Purification over silca gel eluting with pet-ether:DCM (4:1) gave title compound (0.27 g, 58 %) as a colourless oil.

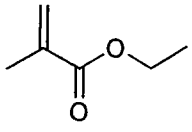
^{1}H-NMR (299.9 MHz) δ 1.17 (3H, t, $^3J_{H-H}$ = 7.2 Hz, C**H**$_3$CH$_2$O), 1.56 (6H, s, (C**H**$_3$)$_2$C), 4.07 (2H, q, $^3J_{H-H}$ = 7.2 Hz, C**H**$_2$CH$_3$O), 7.29-7.60 (5H, m, C$_6$**H**$_5$).

^{13}C-NMR δ 14.2 (1C, s, **C**H$_3$CH$_2$O), 26.6 (1C, s, **C**(CH$_3$)$_2$), 45.6 (2C, s, C(**C**H$_3$)$_2$), 61.2 (1C, s, CH$_3$**C**H$_2$O), 128.9-138.0 (6C, s, **C**$_6$H$_5$), 174.8 (1C, s, **C**=O).

υ (cm^{-1}) 2981, 1721, 1475, 1465, 1264, 1151 and 1114.

m/z (EI) 272 ([M+H]$^+$ 25.4 %), 271 ([M]$^+$, 1.8 %), 198 ([M]$^+$-C(O)OEt, 1.4 %), 156 ([M]$^+$-C(CH$_3$)$_2$C(O)OEt, 51.1 %), 77 ([M]$^+$-SeC(CH$_3$)$_2$C(O)OEt, 28.2 %).

6.2.4 Ethyl methacrylate 32



NaHCO$_3$ (75 mg, 0.8 mmol) and NaIO$_4$ (0.38 mg, 1.8 mmol) were added to a solution of ethyl α-selenophenylisobutyrate (207 mg, 0.8 mmol) in a mixture of methanol (15 ml) and water (2 ml) and the reaction was stirred for 1 h at r.t. The organics were extracted into diethyl ether (3 x 20 ml) washed with NaHCO$_3$ and dried (MgSO$_4$). Diethyl ether was removed by distillation. Ethyl methacrylate was recovered by vacuum transfer (50 mg, 58 %).

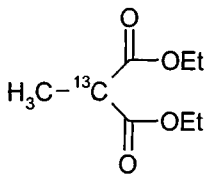
^{1}H-NMR (199.9 MHz) δ 1.25 (3H, t, $^3J_{H-H}$ = 7.1 Hz, C**H**$_3$CH$_2$O), 1.89 (3H, s, C**H**$_3$), 4.15 (2H, q, CH$_3$C**H**$_2$O), 5.50, 6.05 (2H, C=C**H**$_2$)

^{13}C-NMR (100.6 MHz) δ 14.1 (1C, s, **C**H$_3$CH$_2$O), 18.2 (1C, s, **C**H$_3$), 60.5 (1C, s, CH$_3$**C**H$_2$O), 125.0 (1C, s, C=**C**H$_2$), 136.4 (1C, s, **C**=CH$_2$), 167.3 (1C, s, **C**=O).

υ (cm^{-1}) 2985, 1728, 1452 and 1168

m/z (EI) 114 (M$^+$ 4.2 %), 99 ([M]$^+$-CH$_3$ 20.0 %), 69 ([M]$^+$-OEt, 99.2 %), 41 ([M]$^+$-C(O)OEt, 100 %).

6.2.5 Diethyl methyl-[2-^{13}C]-malonate 17a

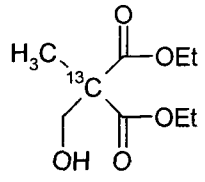


A solution of diethyl [2-^{13}C]-malonate (2.0 g, 12.4 mmol) in THF (5 ml) was added to a suspension of sodium hydride (0.5 g, 12.5 mmol) in THF (36 ml) maintained at 0 °C. When all of the sodium hydride was consumed, a solution of methyl iodide (1.77 g, 12.4 mmol) in THF (3.5 ml) was added and heated to 90 °C for 2 h. The reaction was slowly quenched with ethanol (2 ml) and then water (30 ml) was added. The organics were extracted into diethyl ether (3 x 20 ml), combined, dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (2.15 g, 99 %) as a clear oil. This isotopically labelled product was used directly in the preparation of diethyl (hydroxymethyl)-methyl-[2-^{13}C]-malonate without further purification or characterisation. The ^{1}H and ^{13}C-NMR of diethyl methylmalonate (unlabelled) is described below.

^{1}H-NMR (299.9 MHz) δ 1.26 (6H, t, $^3J_{HH}$ = 7.1 Hz, C**H**$_3$CH$_2$O), 1.39 (3H, d, $^3J_{HH}$ = 6.0 Hz, C**H**$_3$), 3.40 (1H, q, $^3J_{HH}$ = 7.2 Hz, CH$_3$C**H**$_2$O), 4.17 (4H, q, $^3J_{HH}$ = 7.2 Hz, CH$_3$C**H**$_2$O).

^{13}C-NMR (50.3 MHz) δ 13.7 (2C, s, **C**H$_3$CH$_2$O), 14.2 (1C, s, **C**H$_3$), 46.4 (1C, s, **C**), 61.5 (2C, s, CH$_3$**C**H$_2$O), 170.3 (1C, s, **C**=O).

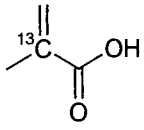
6.2.6 Diethyl (hydroxymethyl)-methyl-[2-^{13}C]-malonate 18a



Diethyl methyl-[2-^{13}C]-malonate (2.15 g, 12.3 mmol) was added to a saturated solution of $NaHCO_3$ (1.61 g, 19.7 mmol) in formaldehyde 37 wt. % (1.53 g, 19.4 mmol) and stirred for 2 h at r.t. Saturated ammonium sulphate (10 ml) solution was then added to the mixture and the organics were extracted into diethyl ether. The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (2.45 g, 97 %) as a clear oil. This material was used directly in the preparation of [2-^{13}C]-methacrylic acid without further purification or charcterisation. The ^{1}H and ^{13}C-NMR of diethyl (hydroxymethyl) methylmalonate (unlabelled) is described below.

^{1}H-NMR (299.9 MHz) δ 1.25 (6H, t, $^3J_{HH}$ = 7.1 Hz, C**H**$_3$CH$_2$O), 1.42 (3H, s, C**H**$_3$), 3.83 (2H, s, C**H**$_2$OH), 4.19 (4H, q, $^3J_{HH}$ = 7.1 Hz, CH$_3$C**H**$_2$O).
^{13}C-NMR (100.6 MHz) δ 13.9 (2C, s, **C**H$_3$CH$_2$O), 17.5 (1C, s, **C**H$_3$), 55.7 (1C, s, **C**), 61.5 (1C, s, **C**H$_2$OH), 66.7 (2C, s, CH$_3$**C**H$_2$O), 171.6 (1C, s, **C**=O).

6.2.7 [2-^{13}C]-Methacrylic acid 15c



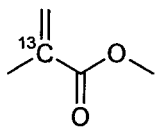
Diethyl (hydroxymethyl)-methyl-[2-^{13}C]-malonate (2.45 g, 11.9 mmol) was added to a solution of 5 % HCl (8 ml) and heated under reflux for 72 h. The organics were extracted into diethyl ether (3 x 15 ml) and combined. The organic extracts were dried ($MgSO_4$) and distilled (35 °C) to remove diethyl ether. Vacuum transfer gave the title

product (1.03 g, 99 %) as a clear oil. This labelled product was used in the preparation methyl [2-^{13}C]-methacrylate without characterisation. The ^{1}H and ^{13}C-NMR of methacrylic acid (unlabelled) is described below.

^{1}H-NMR (299.9 MHz) δ 1.93 (3H, s, C**H**$_3$), 5.65, 6.21 (2H, s, C=C**H**$_2$).

13C-NMR (100.6 MHz) δ 17.8 (1C, s, **C**H$_3$), 127.8 (1C, s, C=**C**H$_2$), 135.7 (1C, s, **C**=CH$_2$), 173.2 (1C, s, **C**=O).

6.2.8 Methyl [2-^{13}C]-methacrylate 1a

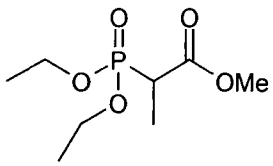


DMAP (0.18 g, 1.5 mmol) was added to a solution of [2-^{13}C]-methacrylic acid (1.03 g, 11.8 mmol) in a mixture of methanol (1.15 ml) and diethyl ether (20 ml) and cooled to 0 °C. Dicyclohexylcarbodiimide (3.26 g, 15.8 mmol) was then added and the solution stirred for 2 h at r.t. The resultant dicyclohexyl urea precipitate was filtered and the diethyl ether was removed by distillation. The isotopically labelled product was isolated by vacuum transfer (282 mg, 24 %) and was moved onto the polymerisation reaction without further purification or characterisation. The ^{1}H and ^{13}C-NMR of methyl methacrylate (unlabelled) is described below.

^{1}H-NMR (299.9 MHz) δ 1.87 (3H, s, C**H**$_3$), 3.69 (3H, s, OC**H**$_3$), 5.49, 6.03 (2H, s, C=C**H**$_2$).

^{13}C-NMR (75.4 MHz) δ 18.5 (1C, s, **C**H$_3$), 51.9 (1C, s, O**C**H$_3$), 125.6 (1C, s, C=**C**H$_2$), 136.4 (1C, s, **C**=CH$_2$), 168.0 (1C, s, **C**=O).

6.2.9 Methyl 2-(diethylphosphono)propionate[3] 39



Methyl 2-bromopropionate (2.52 g, 15.1 mmol) was added to triethyl phosphite (2.5 g, 15.1 mmol) at 130 °C and heated for 16 h. Vacuum distillation (65 °C/0.03 mbar, lit.[3] 95 °C/1 mbar) gave the title compound (2.29 g, 68 %) as a colourless oil.

^{1}H-NMR (400.0 MHz) δ 1.25 (6H, t, $^3J_{H\text{-}H}$ = 7.1 Hz, C**H**$_3$CH$_2$O), 1.34 (3H, dd, $^3J_{H\text{-}P}$ = 10.8 Hz, $^3J_{H\text{-}H}$ = 7.20 Hz, C**H**$_3$), 2.94 (1H, dq, $^2J_{H\text{-}P}$ = 16.2 Hz, $^3J_{H\text{-}H}$ = 7.20 Hz, C**H**), 3.65 (3H, s, OC**H**$_3$), 4.05 (4H, m, CH$_3$C**H**$_2$O).

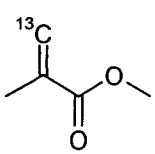
^{13}C-NMR (100.6 MHz) δ 11.5 (1C, d, $^2J_{C\text{-}P}$ = 6.13 Hz, **C**H$_3$), 16.2 (2C, d, $^3J_{C\text{-}P}$ = 5.73 Hz, **C**H$_3$CH$_2$O), 39.0 (1C, d, $^1J_{C\text{-}P}$ = 133.4 Hz, P(O)**C**CH$_3$), 52.2 (1C, s, O**C**H$_3$), 62.5 (2C, d, $^2J_{C\text{-}P}$ = 6.8 Hz, CH$_3$**C**H$_2$O), 170.03 (1C, $^2J_{C\text{-}P}$ = 4.5 Hz, **C**=O).

^{31}P-NMR δ 24.6 (1P, s, **P**=O).

υ (cm^{-1}) 2985, 1740, 1437, 1391, 1320 and 1255.

m/z (EI) 225 ([M+H]$^+$ 55.87 %), 224 (M$^+$, 25.7 %), 209 (M$^+$-CH$_3$, 23.6 %), 193 (M$^+$-OCH$_3$, 53.6), 165 (M$^+$-C(O)OCH$_3$ 57.5 %),138 (M$^+$- C(CH$_3$)C(O)OCH$_3$, 30.9 %),

6.2.10 Methyl [3-^{13}C]-methacrylate 1b



A saturated solution of potassium carbonate (1.36 g, 9.8 mmol) was added to a solution of methyl 2-(diethylphosphono)propionate (1.47 g, 6.6 mmol) in [^{13}C]-formaldehyde 20 wt.% (1.08g, 7.2 mmol) and the reaction was stirred for 24 h at r.t. Brine (10 ml) was

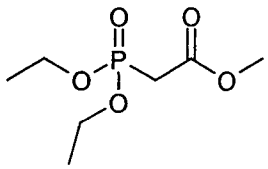
added and the organic layer was extracted into diethyl ether (3 x 10ml). The organic extracts were combined, dried ($MgSO_4$) and the diethyl ether was removed by distillation. The isotopically labelled product was recovered by vacuum transfer (290 mg, 44 %) as a colourless oil.

^{1}H-NMR (200.0 MHz) δ 1.95 (3H, d, $^3J_{H\text{-}C}$ = 5.8 Hz, C**H**$_3$), 3.75 (3H, s, OC**H**$_3$), 6.50-5.70 (1H, d, $^1J_{H\text{-}C}$ =161.2 Hz, C=^{13}C**H**$_2$), 5.96-5.17 (1H, d, $^1J_{H\text{-}C}$ = 158.0 Hz, C=^{13}C**H**$_2$)

^{13}C-NMR (100 MHz) δ 18.3 (1C, s, **C**H$_3$CH$_2$O), 51.8 (1C, s, OCH$_3$), 125.3 (1C, s, C=^{13}**C**H$_2$), 136.2 (1C, d, 71 Hz, **C**=^{13}CH$_2$), 158.2 (1C, s, **C**=O).

m/z (EI) 102 ([M+1+H]$^+$, 8.5 %), 101 ([M+1]$^+$ 54.8 %),

6.2.11 Methyl 2-(diethylphosphono)acetate 56



Triethyl phosphite (8.0 g, 48.2 mmol) and methyl 2-bromoacetate (7.37 g, 48.2 mmol) were heated at 90 °C for 2 h. Vacuum distillation (60 °C/0.05 mbar, lit.[4] 99 °C/1 mmHg) gave title compound (7.57 g, 75 %) as a clear oil.

^{1}H-NMR (200.0 MHz) δ 1.25 (6H, t, $^3J_{H\text{-}H}$ = 7.1 Hz, C**H**$_3$CH$_2$O), 2.95 (2H, d, $^2J_{H\text{-}P}$ = 21.5 Hz), 3.65 (3H, s, OC**H**$_3$), 4.05 (4H, m, CH$_3$C**H**$_2$O).

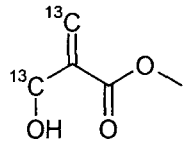
^{13}C-NMR (100.6 MHz) δ 16.0 (2C, d, $^3J_{C\text{-}P}$ = 5.7 Hz, **C**H$_3$CH$_2$O), 33.8 (1C, d, $^1J_{C\text{-}P}$ = 134.3 Hz, P(O)**C**C(O)OCH$_3$), 52.2 (1C, s, OCH$_3$), 62.4 (2C, d, $^2J_{C\text{-}P}$ = 6.0 Hz, CH$_3$**C**H$_2$O), 166.0 (1C, s, **C**=O).

^{31}P-NMR δ 20.7 (1P, s, **P**=O).

υ (cm^{-1}) 2988, 1743, 1483, 1394 and 1275.

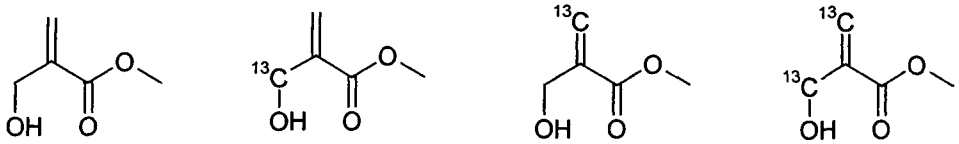
m/z (EI) 210 (M$^+$, 2.1 %), 179 (M$^+$-OCH$_3$, 29.0 %), 151 (M$^+$-C(O)OCH$_3$, 30.3 %), 137 (M$^+$-CH$_2$ C(O)OCH$_3$, 40.2 %),

6.2.12 Methyl [α-^{13}C]-(hydroxymethyl)-[3-^{13}C]-acrylate 41c



[$^{13}C_2$]-MHMA

A saturated solution of potassium carbonate (2.17 g, 15.7 mmol) was added to a solution of methyl 2-(diethylphosphono)acetate (2.22, 14.0 mmol) in a mixture of 20 wt.% [^{12}C]- and [^{13}C]-formaldehyde solution (3.33g, 21.0 mmol and 1.85 g, 11.66 mmol respectively). The reaction mixture was stirred for 1.5 h at r.t. and then saturated ammonium chloride solution (10 ml) was added The organics were extracted into diethyl ether (3 x 15 ml), combined, dried ($MgSO_4$) and concentrated under reduced pressure. Purification over silica gel, eluting with pet-ether:ethyl acetate (2:1) gave the following products (0.50 g, 47 %).

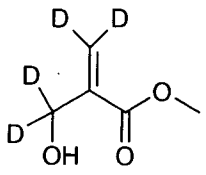


^{1}H-NMR (299.9 MHz) δ 3.75 (3H, s, OC**H**$_3$), 4.30 (2H, d, $^1J_{H\text{-}C}$ = 159.9 Hz, $^3J_{H\text{-}C}$ = 6.2 Hz, ^{13}C**H**$_2$OH), 4.30 (2H, d, $^3J_{H\text{-}C}$ = 6.0 Hz, C**H**$_2$OH), 5.82, 6.23 (2H, s, $^3J_{H\text{-}C}$ = 4.2 Hz, C=C**H**$_2$), 5.74 and 6.23 (1H, d, $^1J_{H\text{-}C}$ = 107.0 Hz, and 1H, d, $^1J_{H\text{-}C}$ = 117.0, C=^{13}C**H**$_2$).

^{13}C-NMR (50.3 MHz) 52.0 (1C, s, O**C**H$_3$), 61.9 (1C, s, **C**H$_2$OH), 61.5-62.4 (1C, d, $^1J_{C\text{-}C}$ = 48.0 Hz, ^{13}**C**H$_2$OH), 125.6 (1C, s, C=**C**H$_2$), 124.8-126.2 (1C, d, $^1J_{C\text{-}C}$ = 71.4 Hz, C=^{13}**C**H$_2$), 139.7 (1C, s, **C**=CH$_2$), 139-140.4 (1C, d, $^1J_{C\text{-}C}$ = 71.0 Hz, **C**=CH$_2$), 139.2-140.1 (1C, d, $^1J_{C\text{-}C}$ = 45.3.0 Hz, **C**=CH$_2$), 166.9 (1C, s, **C**=O).

m/z (EI) 116 (M^+, 1.41 %, CH_2=C(CH_2OH)C(O)OCH_3), 117 ([M+1]$^+$ 0.88 %, $^{13}CH_2$=C(CH_2OH)C(O)OCH_3 and CH_2=C($^{13}CH_2$OH)C(O)OCH_3), 118 ([M+2]$^+$ 0.41%, $^{13}CH_2$=C($^{13}CH_2$OH)C(O)OCH_3).

6.2.13 Methyl [α-$^2H_2$]-(hydroxymethyl)-[3-$^2H_2$]-acrylate 41d



[$^2H_4$]-MHMA

A saturated solution of potassium carbonate (2.17 g, 15.7 mmol) was added to a solution of methyl 2-(diethylphosphono)acetate (1.89 g, 9.0 mmol) in [$^2H_2$]-formaldehyde 20 wt.% (5.41 g, 33.8 mmol) and stirred for 1.5 h at r.t. Ammonium chloride solution (10 ml) was added and the organics were extracted into diethyl ether (3 x 15 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Purification over silica gel eluting with pet-ether:ethyl acetate (2:1) gave the title compound (0.78 g, 73 %) as a colourless oil.

^{1}H-NMR (200.0 MHz) δ 3.73 (3H, s, OC**H**$_3$).

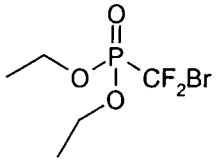
^{2}H-NMR (46.0 MHz) δ 4.30 (2D, s, C**D**$_2$OH), 5.87, 6.28 (2D, s, C**D**$_2$=C).

^{13}C-NMR (100.57 MHz) δ 51.8 (1C, s, O**C**H$_3$), 61.1-62 (1C, p, **C**D$_2$OH), 125-126 (1C, p, **C**D$_2$=C), 139.0 (1C, s, CD$_2$=**C**), 166.7 (1C, s, **C**=O).

υ (cm^{-1}) 3000-3600, 2955, 2189, 2102, 1720, 1599, 1438, 1317, 1280 and 1203.

m/z (EI) 120 ([M+1]$^+$ 1.3 %), 89 ([M+1]$^+$-OCH$_3$, 86.8 %), 89 ([M+1]$^+$-CD$_2$OH, 86.8 %), 72 [M+1]$^+$-C(O)OCH$_3$, 2.4 %), 59 ([M+1]$^+$-CD$_2$=CCD$_2$OH, 40.1 %).

6.2.14 Diethyl bromodifluoromethanephosphonate[5] 83



Dibromodifluoromethane (61.64 g, 293.8 mmol) was added to a solution of triethylphosphite (46 g, 276.8 mmol) in dry diethyl ether (120 ml) at 0 °C and stirred for 21 h at 40 °C. The reaction mixture was concentrated under reduced pressure and distilled (45 °C/0.04 mbar, lit.[5] 99-102 °C/16 mmHg) to give the title compound (68 g, 92 %) as a clear oil.

^{1}H-NMR (400 MHz) δ 1.37 (6H, t, $^{3}J_{H\text{-}H}$ = 7.0 Hz, C**H**$_3$CH$_2$O), 4.32 (4H, m, CH$_3$C**H**$_2$O).

^{13}C-NMR (100.6 MHz) δ 16.2 (2C, d, $^{3}J_{C\text{-}P}$ = 5.8 Hz, **C**H$_3$CH$_2$O), 66.2 (2C, d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, CH$_3$**C**H$_2$O), 116.6 (1C, td, $J_{C\text{-}F}$ = 328.8 Hz, $J_{C\text{-}P}$ = 238.2 Hz, P**C**F$_2$).

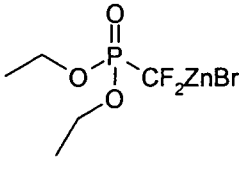
^{19}F-NMR (376.3 MHz) δ -61.5 (2F, d, $J_{F\text{-}P}$ = 93.3 Hz).

^{31}P-NMR (161.9 MHz) δ 2.3 (1P, t, $J_{P\text{-}F}$ = 93.4, **P**=O)

υ (cm^{-1}) 1279, 1140, 1087 and 1009.

m/z (CI^{+}) 286 (M+NH$_4$)$^{+}$, 97.2 %), 284 (M+NH$_4$)$^{+}$, 100.0 %)

6.2.15 [(Diethoxyphosphinyl)difluoromethyl]zinc bromide[6] 84



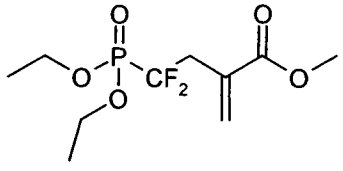
Diethyl bromodifluoromethanephosphonate (2.98g, 11.2 mmol) was added to acid washed zinc powder (0.73 g, 11.2 mmol) in dry monoglyme (25 ml). The solution was

stirred for 1 h at 45 °C and filtered to remove excess zinc powder. The organozinc reagent was sufficiently stable in solution to obtain ^{19}F- and ^{31}P-NMR analysis.

^{19}F-NMR (235.3 MHz) δ -128.43 (2F, d, $J_{F\text{-}P}$ = 92.0 Hz, CF_2).

^{31}P-NMR (101.3 MHz) δ 13.4 (1P, t, $J_{P\text{-}F}$ = 93.0 Hz, P=O).

6.2.16 Methyl 4,4-difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoate[7] 75



Methyl 2-(bromomethyl)acrylate (2 g, 11.2 mmol) was added slowly to a solution of copper(I) bromide (8 mg, 56 mmol) in [(diethoxyphosphinyl)difluoromethyl]zinc bromide (prepared *via* the above procedure) and stirred for 1 h at 30 °C. The solution was concentrated under reduced pressure, washed with water (20 ml) and extracted into DCM (3 x 20 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Purification over silica gel eluting with pet-ether:ethyl acetate (3:1) gave the title compound (1.66 g, 52 %) as a colourless oil.

^{1}H-NMR (400 MHz) δ 1.36 (6H, t, $^3J_{H\text{-}H}$ = 7.2 Hz, CH_3CH_2O), 3.14 (2H, td, $^3J_{H\text{-}P}$ = 4.7, $^3J_{H\text{-}F}$ = 19.8 Hz, CF_2CH_2), 3.76 (3H, s, OCH_3), 4.25 (4H, m, CH_3CH_2O), 5.86, 6.44 (2H, s, $C=CH_2$).

^{13}C-NMR (100.6 MHz) δ 16.3 (2C, d, $^3J_{C\text{-}P}$ = 5.3 Hz, CH_3CH_2O), 35.0 (1C, m, CF_2CH_2), 52.2 (s, OCH_3), 64.6 (2C, d, $^2J_{C\text{-}P}$ = 6.4 Hz, CH_3CH_2O), 118.9 (1C, td, $^1J_{C\text{-}F}$ = 261.3 Hz, $^1J_{C,P}$ = 216.0 Hz, CF_2CH_2), 130.5 (s, $C=CH_2$), 131.4 (s, $C=CH_2$), 166.6 (s, C=O).

^{31}P-NMR (161.9 MHz) δ 9.6 (1P, t, $J_{P\text{-}F}$ = 106.5 Hz, P=O).

^{19}F-NMR (376.3 MHz) δ -111.8 (1F, dt, $^2J_{F\text{-}P}$ = 106.9 Hz, $^3J_{F\text{-}H}$ = 19.7 Hz, CF_2CH_2).

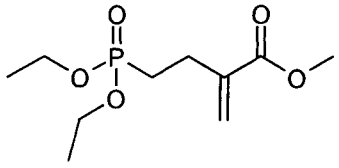
m/z (EI^+) 286 ($[M]^+$ 28.7 %,), 255 ($[M]^+$ -OCH_3, 33.5 %), 227 ($[M]^+$ -$C(O)OCH_3$), 201 ($[M]^+$-CH_2=$CC(O)OCH_3$, 1.9 %), 149 ($[M]^+$-$(OEt)_2P(O)$ 17.0 %), 99 ($[M]^+$-$(OEt)_2P(O)CF_2$, 16.1 %).

υ (cm^{-1}) 2987, 1727, 1635, 1440, 1310, 1276 and 1163.

HRMS calculated for $C_{10}H_{17}F_2O_5P$: 286.07820, found: 286.07820.

Elemental analysis calculated for $C_{10}H_{17}F_2O_5P$: C, 41.96 %; H, 5.99 %, found C, 40.96 %; H, 6.07 %).

6.2.17 Methyl 4-(diethoxyphosphinoyl)-2-methylenebutanoate 74



n-Butyllithium 1.6 M in hexane (4.04 ml, 6.5 mmol) was added slowly to a solution of diisopropylamine (1.01 ml, 7.1 mmol) in THF (10 ml) at 0 °C. After cooling to -78 °C, a solution of diethyl methylphosphonate (0.89 g, 5.9 mmol) in THF (9 ml) was added and stirred for 30 min. Methyl 2-(bromomethyl)acrylate (1.13 g, 6.3 mmol) was added slowly and stirred for 0.5 h at this temperature. Stirring was continued for a further 1 h at r.t. Water (10 ml) was added and the organics were extracted into DCM (3 x 10 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Purification over silica gel eluting with a mixture of ethyl acetate:pet-ether (2:1) gave the title compound (0.52 g, 35 %) as a yellow oil

^{1}H-NMR (400 MHz) δ 1.30 (6H, t, $^3J_{H,H}$ = 7.0 Hz, C**H**$_3$CH$_2$O), 1.91 (2H, m, P(O)C**H**$_2$), 2.56 (2H, m, C**H**$_2$C=O), 3.74 (3H, s, OC**H**$_3$), 4.07 (4H, m, CH$_3$C**H**$_2$O), 5.60, 6.17 (1H, s, C=C**H**$_2$).

^{13}C-NMR (100.6 MHz) δ 16.4 (2C, d, $^3J_{C\text{-}P}$ = 6.1 Hz, **C**H$_3$CH$_2$O), 24.4 (1C, d, $^1J_{C\text{-}P}$ = 142.6 Hz, P(O)**C**H$_2$), 25.4 (1C, d, $^2J_{C\text{-}P}$ = 3.8 Hz, P(O)CH$_2$**C**H$_2$), 51.9 (1C, s, O**C**H$_3$), 61.6 (2C, d, $^2J_{C\text{-}P}$ = 6.4 Hz, CH$_3$**C**H$_2$O), 125.7 (1C, s, C=**C**H$_2$), 139.2 (d, $^3J_{C\text{-}P}$ = 17.6 Hz, **C**=CH$_2$), 166.9 (s, **C**=O).

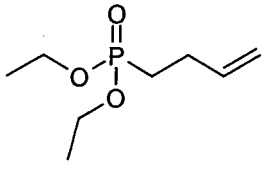
^{31}P(161.90 MHz) δ 33.9 (1P, s, **P**=O).

m/z (EI^+) 250 ($[M]^+$ 4.8 %), 219 ($[M]^+$ -OCH_3, 12.7 %), 191 ($[M]^+$ -$C(O)OCH_3$, 56.8 %), 165 ($[M]^+$ -$C{=}CH_2C(O)OCH_3$, 3.9 %), 113 ($[M]^+$ -P(O)OEt, 4.4 %).

υ (cm^{-1}) 2980, 1718, 1633, 1438 and 1243.

Elemental analysis calculated for $C_{10}H_{19}O_5P$: C, 46.23 %; H, 7.94 %, found C, 46.20; % H, 7.65 %.

6.2.18 Diethyl but-3-enephosphonate[8] 92



n-Butyllithium 1.6 M in hexane (20.54 ml, 32.9 mmol) was added slowly to a solution of diisopropylamine (5.07 ml, 36.2 mmol) in THF (50 ml) at 0 °C. The mixture was cooled to -78 °C and diethyl methylphosphonate (5.0 g, 32.9 mmol) in THF (50 ml) was added and stirred for 30 min. Allylbromide (5.96 g, 49.3 mmol) was added slowly at this temperature and stirred for 10 min. The reaction mixture was warmed and stirred for 1 h at r.t. Water (40 ml) was added and the organic layer was extracted into DCM (3 x 15 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Distillation (36 °C/0.02 mbar, lit.[8] 70 °C/1 Torr) gave the title compound (3.8 g, 60%) as a colourless oil.

^1H (400 MHz) δ 1.30 (6H, t, $^3J_{H\text{-}H}$ = 7.4 Hz, CH_3CH_2O), 1.79 (2H, m, $P(O)CH_2$), 2.32 (2H, m, $P(O)CH_2CH_2$), 4.07 (4H, m, CH_3CH_2O), 5.01 (2H, m, $CH{=}CH_2$), 5.84 (1H, m, $CH{=}CH_2$).

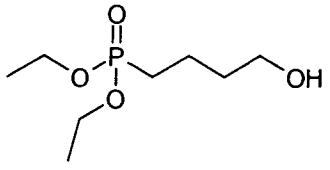
^{13}C (100.6 MHz) δ 16.4 (2C, d, $^3J_{C\text{-}P}$ = 5.7 Hz, CH_3CH_2O), 24.9 (1C, d, $^1J_{C\text{-}P}$ = 140.8 Hz, $P(O)CH_2$), 26.5 (1C, d, $^2J_{C\text{-}P}$ = 4.5Hz, $P(O)CH_2CH_2$), 61.4 (2C, d, $^2J_{C\text{-}P}$ = 6.5 Hz, CH_3CH_2O), 115.0 (s, $CH{=}CH_2$), 137.2 (d, $^3J_{C\text{-}P}$ 17.6 Hz, $CH{=}CH_2$).

^{31}P (161.9 MHz) δ 34.7 (1P, s, P=O).

υ (cm^{-1}) 2910, 1642, 1445, 1285 and 1369.

m/z (EI^+) 192 ($[M]^+$ 7.9 %), 55 ($[M]^+$ $(OEt)_2P(O)$, 86.6 %), 41($[M]^+$ $(OEt)_2P(O)CH_2$, 20.1 %)

6.2.19 Diethyl 4-hydroxybutylphosphonate 93



A solution of 2-methyl-2-butene (0.59 g, 8.4 mmol) in THF (0.9 ml) was added to sodium borohydride (0.24 g, 6.3 mmol) and cooled to -20 °C. A solution of boron trifluoride etherate (0.53 ml, 4.2 mmol) was added to the reaction mixture which was then stirred for 1 h. A solution of diethyl but-3-enephosphonate (0.40 g, 2.1 mmol) was then added and the reaction was warmed to r.t. After stirring for 2.5 h, the organoboranes were oxidised by successively adding, water (1 ml), sodium hydroxide 6 M (1.15 ml) and hydrogen peroxide 30 wt. % (1.15 ml). The reaction mixture was stirred for 3 h at r.t. and water (15 ml) was added. The organic layer was extracted into Et_2O (3 x 15 ml), combined, dried ($MgSO_4$) and concentrated under reduced pressure. Purification over silica gel eluting with ethanol:ethyl acetate (1:7) gave the title compound (0.14 g, 32 %) as a clear oil.

^{1}H-NMR (400 MHz) δ 1.32 (6H, t, $^3J_{H,H}$ = 7.2 Hz, $OCH_2C\mathbf{H}_3$), 1.67 (2H, m, $P(O)C\mathbf{H}_2$), 1.74 (2H, m, $P(O)CH_2C\mathbf{H}_2$), 1.80 (2H, m, $P(O)CH_2CH_2C\mathbf{H}_2$), 3.67 (2H, t, $^3J_{H-H}$ = 6.0 Hz, $C\mathbf{H}_2OH$), 4.09 (4H, m, $OC\mathbf{H}_2CH_3$)

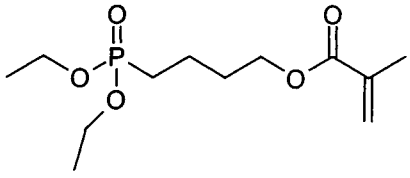
^{13}C-NMR (100.6 MHz) δ 16.3 (2C, d, $^3J_{C-P}$ = 5.03 Hz, $OCH_2\mathbf{C}H_3$), 18.7 (1C, d, $^3J_{C-P}$ = 5.0 Hz, $P(O)CH_2CH_2\mathbf{C}H_2$), 25.1 (1C, d, $^1J_{C-P}$ = 140.7 Hz, $P(O)\mathbf{C}H_2$), 33.1 (1C, d, $^2J_{C-P}$ = 14.9 Hz, $P(O)CH_2\mathbf{C}H_2$), 61.4 (2C, d, $^2J_{C-P}$ = 6.4 Hz, $O\mathbf{C}H_2CH_3$), 61.9 (s, $\mathbf{C}H_2OH$).

^{31}P (161.9 MHz) 35.53 (1P, s, **P**=O).

υ (cm^{-1}) 3200-3500, 2978, 2940, 1225, 1056, and 1027.

m/z (EI$^+$) 210 ([M]$^+$ 0.1 %), 193 (M$^+$ -OH, 3.8 %), 179 (M$^+$ -CH_2OH, 17.6 %), 137 (M$^+$ -$CH_2CH_2CH_2CH_2OH$, 100 %).

6.2.20 4-(Diethylphosphinoyl)butyl methacrylate 76



A solution of diethyl 4-hydroxybutylphosphonate (210 mg, 1.0 mmol) in DCM (15 ml) and triethylamine (distilled and dried over KOH, 0.14 ml, 1.0 mmol) were added successively to dimethylaminopyridine (0.12 mg, 10 x 10^{-7} mmol). The reaction mixture was cooled to 0 °C and methacryloyl chloride (128 mg, 0.12 mmol) was added and then warmed to r.t. and stirred for 12 h. Further additions of triethylamine (0.06ml, 0.5 mmol) and methacryolyl chloride (0.05 ml, 0.5 mmol) were added to consume the remaining diethyl 4-hydroxybutylphosphonate. After stirring for 1 h at r.t., water (20 ml) was added and the organics were extracted into Et_2O (3 x 20 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Purification over silica gel eluting with ethyl acetate gave the title compound (0.229 g, 45 %) as a light yellow oil.

^{1}H-NMR (400 MHz) δ 1.30 (6H, t, $^3J_{H\text{-}H}$ = 7.2 Hz, OCHC**H$_3$**), 1.63-1.78 (6H, m, P(O)C**H$_2$**C**H$_2$**C**H$_2$**), 1.91 (3H, s, C**H$_3$**), 4.04-4.13 (6H, m, OC**H$_2$**CH$_3$, C**H$_2$**O), 5.53, 6.07 (2H, s, C**H$_2$**=C).

^{13}C-NMR (100.6 MHz) δ 16.4 (2C, d, $^3J_{C\text{-}P}$ = 6.0 Hz, OCH$_2$**C**H$_3$), 18.3 (1C, s, **C**H$_3$), 19.2 (d, $^3J_{C\text{-}P}$ = 5.3 Hz, P(O)CH$_2$CH$_2$**C**H$_2$), 25.2 (1C, d, $^1J_{C\text{-}P}$ = 141.5 Hz, P(O)**C**H$_2$), 29.3 (1C, d, $^2J_{C\text{-}P}$ = 16.8 Hz, P(O)CH$_2$**C**H$_2$CH$_2$), 61.5 (2C, d, $^2J_{C\text{-}P}$ 6.5 Hz, O**C**H$_2$CH$_3$), 63.8 (1C, s, **C**H$_2$O), 125.4 (s, C=**C**H$_2$), 136.3 (s, **C**=CH$_2$), 167.3 (s, **C**=O).

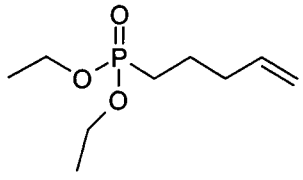
^{31}P (161.9 MHz) δ 34.8 (1P, s, **P**=O).

m/z (EI^+) 278 (M^+ 2.37 %), 193 (M^+ -$OC(O)CCH_2CH_3$, 24.86 %), 137 (M^+ -113, $(CH_2)_4OC(O)CCH_2CH_3$, 16.81 %).

υ (cm^{-1}) 2981, 1719, 1637, 1453, 1391, 1320 and 1297.

HRMS calculated for $C_{12}H_{23}O_5P$: 278.1283, found 278.1283.

6.2.21 Diethyl 4-pent-1-enylphosphonate[9] 96



5-Bromopent-1-ene (3.5 g, 23.5 mmol) and triethyl phosphite (15.61 g, 93.9 mmol) were heated under reflux for 17 h. Distillation (55 °C/0.03 mbar, lit.[10] 53 °C/0.05 mmHg) gave title compound (3.53 g, 73 %) as a colourless oil.

^1H (400 MHz) δ 1.28 (6H, t, $^3J_{H\text{-}H}$ = 7.3 Hz, CH_3CH_2O), 1.64-1.71 (4H, m, $P(O)CH_2CH_2$), 2.10 (2H, m, $P(O)CH_2$), 4.07 (4H, m, CH_3CH_2O), 5.01 (2H, m, $CH=CH_2$), 5.85 (1H, m, $CH=CH_2$).

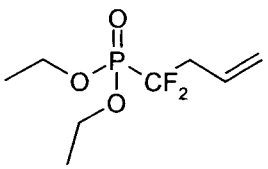
^{13}C (100.6 MHz) δ 16.4 (2C, d, $^3J_{C\text{-}P}$ = 5.8 Hz, CH_3CH_2O), 21.6 (1C, d, $^3J_{C\text{-}P}$ = 4.5 Hz, $P(O)CH_2CH_2CH_2$), 24.9 (1C, d, $^1J_{C\text{-}P}$ = 140.9 Hz, $P(O)CH_2$), 34.3 (1C, d, $^2J_{C\text{-}P}$ = 17.5 Hz, $P(O)CH_2CH_2$), 61.3 (2C, d, $^2J_{C\text{-}P}$ = 6.6 Hz, CH_3CH_2O), 115.6 (s, $CH=CH_2$), 137.3 (s, $CH=CH_2$).

^{31}P (161.9 MHz) δ 33.4 (1P, s, P=O).

υ (cm^{-1}) 2981, 1641, 1240, 1057, 1029 and 960.

m/z (EI^+) 206 ($[M]^+$ 12.2 %), 165 ($[M]^+$-$CH_2CH=CH_2$, 9.3 %), 151 ($[M]^+$-$CH_2CH_2CH=CH_2$ 19.1 %), 137 ($[M]^+$-$CH_2CH_2CH_2CH=CH_2$ 16.1 %).

6.2.22 Diethyl 1,1-difluorobut-3-enylphosphonate[6] 99



[(Diethoxyphosphinyl)difluoromethyl]zinc bromide (2.98 g, 11.2 mmol) prepared as described in **Section 6.2.15** was added to Cu(I)Br (8 mg, 56 mmol). Allyl bromide (2.15 g, 11.2 mmol) was slowly added and stirred for 12 h at r.t. The reaction mixture was concentrated under reduced pressure, washed with water (10 ml) and extracted into DCM (2 x 10 ml). The organic layers were combined, dried ($MgSO_4$) and distilled (55-58 °C/0.09 mbar, lit.[6] 34 °C/0.03 mbar) to give the title compound (1.36 g, 55 %) as a colourless oil.

^{1}H-NMR (200 MHz) δ 1.33 (6H, t, $^3J_{H,H}$ = 7.1, $OCH_2C\mathbf{H}_3$), 2.78 (2H, m, $CF_2C\mathbf{H}_2$), 4.22 (4H, m, $OC\mathbf{H}_2CH_3$), 5.21-5.267 (2H, m, $CH{=}C\mathbf{H}_2$), 5.75-5.86 (1H, m, $C\mathbf{H}{=}CH_2$).

^{13}C-NMR (100.6 MHz) δ 16.3 (2C, d, $^3J_{H\text{-}H}$ = 5.3 Hz, $OCH_2\mathbf{C}H_3$), 38.6 (1C, dt, $^2J_{C\text{-}F}$ = 21.4 Hz, $^2J_{C\text{-}P}$ = 15.3 Hz, $CF_2\mathbf{C}H_2$), 64.3 (2C, d, $^2J_{C\text{-}P}$ = 6.8 Hz, $O\mathbf{C}H_2CH_3$), 119.5 (1C, dt, $^1J_{C\text{-}F}$ = 260.4 Hz, $^1J_{C\text{-}P}$ = 214.5 Hz, P(O)**C**F2), 121.7 (1C, s, CH=**C**H2), 126.8 (1C, q, $^4J_{C\text{-}F/P}$ = 5.5 Hz, $\mathbf{C}H{=}CH_2$).

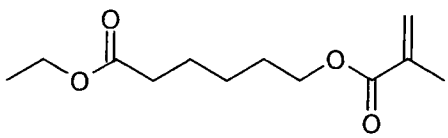
^{19}F-NMR (376.3 MHz) δ -111.3 (2F, dt, $^2J_{F\text{-}P}$ = 107.5 Hz, $^3J_{H\text{-}F}$ =19.4 Hz, P(O)$C\mathbf{F}_2$).

^{31}P-NMR (161.9 MHz) δ 10.0 (1P, t, $^2J_{F\text{-}P}$ = 107.5 Hz, **P**=O)

υ (cm^{-1}) 2988, 1646, 1261, 1014 and 793.

m/z (CI) 229 ($[M+H]^+$ 45.6 %), 246 ($[M+NH_4]^+$ 100 %)

6.2.23 Ethyl 6-hydroxyhexanoate methacrylate 100



A solution of ethyl 6-hydroxyhexanoate (2.0 g, 12.5 mmol) in DCM (distilled, 65 ml) and triethylamine (distilled and dried over KOH, 8 ml, 57.4 mmol) were added successively to dimethylaminopyridine (1.28 g, 10.5 mmol). The reaction mixture was cooled to 0 °C and methacrolyl chloride (1.82 ml, 18.7 mmol) was added and then warmed to r.t. and stirred for 2 h. The reaction mixture was washed with dilute HCl and was extracted into DCM. The organic layer was washed with $NaHCO_3$, combined, dried ($MgSO_4$), and concentrated under reduced pressure. Distillation (52 °C/0.03 mbar) gave the tittle compound (2.06 g, 72 %) as a clear oil.

^{1}H-NMR (299.9 MHz) δ 1.22 (3H, t, $^3J_{H\text{-}H}$ = 7.3 Hz, $OCH_2C\mathbf{H}_3$), 1.41 (2H, m, $EtOC(O)CH_2CH_2C\mathbf{H}_2$), 1.67 (4H, q, $EtOC(O)CH_2C\mathbf{H}_2$, $EtOC(O)CH_2CH_2CH_2C\mathbf{H}_2$), 1.91 (3H, s, $C\mathbf{H}_3$), 2.28 (2H, t, $EtOC(O)C\mathbf{H}_2$), 4.12 (4H, $OC\mathbf{H}_2CH_3$, $C\mathbf{H}_2OC(O)C{=}CH_2CH_3$), 5.52, 6.06 (2H, s, $C{=}C\mathbf{H}_2$).

^{13}C-NMR (75.4 MHz) δ 14.2 (1C, s, $\mathbf{C}H_3CH_2O$), 18.3 (1C, s, $\mathbf{C}H_3$), 24.5 (1C, s, $EtOC(O)CH_2CH_2\mathbf{C}H_2$), 25.5 (1C, s, $EtOC(O)CH_2\mathbf{C}H_2$), 28.3 (1C, s, $EtOC(O)CH_2CH_2\mathbf{C}H_2$), 34.1 (1C, s, $EtOC(O)\mathbf{C}H_2$), 60.2 (1C, s, $CH_3\mathbf{C}H_2O$), 125.7 (1C, s, $C{=}\mathbf{C}H_2$), 136.4 (1C, s, $\mathbf{C}{=}CH_2$), 167.4 (1C, s, $EtO\mathbf{C}(O)CH_2$), 173.4 (1C, s, $O\mathbf{C}(O)C{=}CH_2CH_3$).

υ (cm^{-1}) 2953, 1735, 1637, 1453, 1374, 1320, 1297, 1165, 1097 and 1032

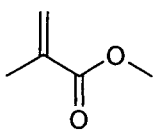
m/z (CI) 246 ($[M+NH_4]^+$ 100 %), 229 ($[M+H]^+$ 98 %).

HRMS calculated for $C_{12}H_{20}O_4$: 246.1705, found 246.1705.

Elemental analysis calculated for $C_{12}H_{20}O_4$: C, 63.31 %; H, 8.86 %, found C, 63.47; % H, 8.87 %.

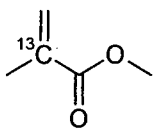
6.3 Polymerisations of methyl methacrylate, methyl [2-^{13}C]- and [3-^{13}C]-methacrylate

The appropriate monomer as indicated in the **Table 20** below was heated in toluene at 80 °C for 4 h using AIBN (0.5 wt.%) as the initiator. In all cases, the viscous liquid obtained was dissolved in toluene and the precipitated from hexane. The polymer was then filtered and dried (80 °C) to constant weight under vacuum.



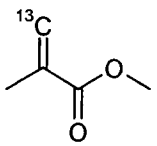
1

methyl methacrylate



1a

methyl [2-^{13}C]-methacrylate



1b

methyl [2-^{13}C]-methacrylate

Monomer (mg)	Toluene (ml)	Yield (%)	Mw	Mn	Mw/Mn
Methyl methacrylate (275 mg)	0.85 ml	77 mg, (28 %)	49000	24000	2.04
Methyl [2-^{13}C]-methacrylate (262 mg)	0.85 ml	90 mg, (34 %)	51000	29000	1.76
Methyl [3-^{13}C]-methacrylate (275 mg)	0.85 ml	62.5 mg, (23 %)	55000	31000	1.77

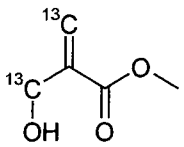
Table 20 Polymerisation conditions and yields.

^{13}C-NMR (100.6 MHz) of poly(methyl [2-^{13}C]-methacryalte). [^{13}C]-enriched peaks are, δ 44.8 *rr*, 45.1 *mr*, 45.8 *mm*

^{13}C-NMR (100.6 MHz) of poly(methyl [3-^{13}C]-methacryalte). [^{13}C]-enriched peaks are between δ 51.7-53.4.

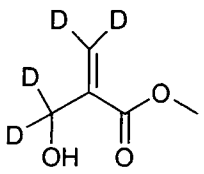
For full assignment of the ^{13}C-NMR spectrum, refer to Chapter 4, **Figure 14**

6.4 Copolymerisations of MHMA, [$^2H_4$]-MHMA and [$^{13}C_2$]-MHMA with MMA



41c

[$^{13}C_2$]-MHMA



41d

[$^2H_4$]-MHMA

The appropriate monomer as indicated in the **Table 21** below was heated with MMA to 80 °C for 2 h using AIBN (0.5 wt.%) as the initiator. The gelled material was dissolved in chloroform and precipitated in hexane. The copolymer was filtered and dried (80 °C) to constant weight under vacuum.

M_1	M_2	Yield (%)	Mw	Mn	Mw/Mn
MMA (480 mg)	MHMA (371 mg)	552 mg (65 %)	164000	62000	2.6
MMA (491 mg)	[$^{13}C_2$]-MHMA (433 mg)	501 mg (54 %)	108000	46000	2.3
MMA (551 mg)	[$^2H_4$]-MHMA (441 mg)	663 mg (67 %)	383000	99000	3.9

Table 21 Results of the copolymerisation.

The copolymer of MMA/MHMA is not random or alternating and consists of small sequences of each monomer units. The [^{13}C]-enriched peaks in the copolymer of ^{13}C-NMR (100.6 MHz) of MMA/[$^{13}C_2$]-MHMA are;

δ 41-44 $^{13}CH_2$-groups of the polymer backbone of [$^{13}C_2$]-MHMA blocks.

δ 47-50 $CH_2/^{13}CH_2$-groups of the copolymer backbone of MMA/[$^{13}C_2$]-MHMA.

δ 58.5-63 $^{13}CH_2OH$.

For detailed assignment, refer to Chapter 4, **Figure 26**.

6.5 Lactonisation of MMA/MHMA, MMA/[$^{13}C_2$]-MHMA and MMA/[$^{2}H_4$]-MHMA copolymers.

DCM (3 ml), followed by conc. HCl (0.15 ml) were added to a solution of the copolymer (300 mg) in a mixture of methanol and toluene (6ml, 50:50) and heated to 80 °C for 45 min. The reaction mixture was precipitated into hexane and dried (80 °C) to constant weight under vacuum, see **Table 22**.

Copolymer (mg)	Yield (%)	Mw	Mn	Mw/Mn
MMA /MHMA (300 mg)	203 mg (68 %)	27000	17000	1.6
MMA/[$^{13}C_2$]-MHMA (300 mg)	232 mg (77 %)	22000	13000	1.7
MMA/[$^{2}H_4$]-MHMA (300 mg)	234 mg (78 %)	58000	29000	2.0

Table 22 Results of the lactonisation reaction.

The [^{13}C]-enriched peaks in the ^{13}C-NMR (100.6 MHz) of lactonised MMA/[$^{13}C_2$]-MHMA copolymer;

δ 37.5-51 Quaternary carbons and CH_2/$^{13}CH_2$-groups of the copolymer backbone of MMA/[$^{13}C_2$]-MHMA.

δ 32-35 $^{13}CH_2$ of the polymer backbone of [$^{13}C_2$]-MHMA blocks.

δ 70-76 $^{13}CH_2O$-group in the lactone.

For detailed assignment, refer to Chapter 4, **Figure 28**.

6.6 References

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